UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-Q

(Mark One)

☒ QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the Quarterly Period Ended March 31, 2023

OR

☐ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF SECURITIES EXCHANGE ACT OF 1934

For the transition period from _____ to _____

Commission file number 000-19125

Ionis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

Delaware	**33-0336973**
(State or other jurisdiction of incorporation or organization)	(IRS Employer Identification No.)
2855 Gazelle Court, Carlsbad, California	**92010**
(Address of Principal Executive Offices)	(Zip Code)

760-931-9200

(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading symbol	Name of each exchange on which registered
Common Stock, $.001 Par Value	"IONS"	The Nasdaq Stock Market LLC

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large Accelerated Filer ☒	Accelerated Filer ☐
Non-accelerated Filer ☐	Smaller Reporting Company ☐ Emerging Growth Company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12(b)-2 of the Securities Exchange Act of 1934). Yes ☐ No ☒

The number of shares of voting common stock outstanding as of April 27, 2023 was 143,092,117.

IONIS PHARMACEUTICALS, INC.
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TRADEMARKS

"Ionis," the Ionis logo, and other trademarks or service marks of Ionis Pharmaceuticals, Inc. appearing in this report are the property of Ionis Pharmaceuticals, Inc. "Akcea," the Akcea logo, and other trademarks or service marks of Akcea Therapeutics, Inc. appearing in this report are the property of Akcea Therapeutics, Inc., Ionis' wholly owned subsidiary. This report contains additional trade names, trademarks and service marks of others, which are the property of their respective owners. Solely for convenience, trademarks and trade names referred to in this report may appear without the ® or TM symbols.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED BALANCE SHEETS
(in thousands, except share data)

	March 31, 2023 (unaudited)	December 31, 2022
ASSETS		
Current assets:		
Cash and cash equivalents	$ 309,031	$ 276,472
Short-term investments	2,037,750	1,710,397
Contracts receivable	13,914	25,538
Inventories	22,200	22,033
Other current assets	159,724	168,254
Total current assets	2,542,619	2,202,694
Property, plant and equipment, net	85,158	74,294
Right-of-use assets	179,148	181,544
Deposits and other assets	78,296	75,344
Total assets	$ 2,885,221	$ 2,533,876
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 10,499	$ 17,921
Accrued compensation	18,160	49,178
Accrued liabilities	112,702	140,101
Income taxes payable	17,286	6,249
Current portion of deferred contract revenue	92,335	90,577
Other current liabilities	8,239	7,535
Total current liabilities	259,221	311,561
Long-term deferred contract revenue	272,973	287,768
0 percent convertible senior notes, net	623,025	622,242
0.125 percent convertible senior notes, net	545,053	544,504
Liability related to sale of future royalties, net	505,081	—
Long-term lease liabilities	177,000	178,941
Long-term mortgage debt	8,811	8,847
Long-term obligations	7,487	7,126
Total liabilities	2,398,651	1,960,989
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 143,022,539 and 142,057,736 shares issued and outstanding at March 31, 2023 (unaudited) and December 31, 2022, respectively	143	142
Additional paid-in capital	2,089,358	2,059,850
Accumulated other comprehensive loss	(48,983)	(57,480)
Accumulated deficit	(1,553,948)	(1,429,625)
Total stockholders' equity	486,570	572,887
Total liabilities and stockholders' equity	$ 2,885,221	$ 2,533,876

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS
(in thousands, except for per share amounts)
(Unaudited)

	Three Months Ended March 31,	
	2023	**2022**
Revenue:		
Commercial revenue:		
SPINRAZA royalties	$ 50,247	$ 53,818
TEGSEDI and WAYLIVRA revenue, net	6,478	6,160
Licensing and other royalty revenue	11,043	12,307
Total commercial revenue	67,768	72,285
Research and development revenue:		
Collaborative agreement revenue	38,334	49,784
Eplontersen joint development revenue	24,422	19,850
Total research and development revenue	62,756	69,634
Total revenue	130,524	141,919
Expenses:		
Cost of sales	1,343	4,170
Research, development and patent	197,813	161,126
Selling, general and administrative	45,516	34,127
Total operating expenses	244,672	199,423
Loss from operations	(114,148)	(57,504)
Other income (expense):		
Investment income	18,627	1,993
Interest expense	(1,608)	(2,122)
Interest expense related to sale of future royalties	(15,515)	—
Loss on investments	(529)	(6,625)
Other income	230	187
Loss before income tax expense	(112,943)	(64,071)
Income tax expense	(11,380)	(1,094)
Net loss	$ (124,323)	$ (65,165)
Basic and diluted net loss per share	$ (0.87)	$ (0.46)
Shares used in computing basic and diluted net loss per share	142,735	141,599

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(in thousands)
(Unaudited)

	Three Months Ended March 31,	
	2023	**2022**
Net loss	$ (124,323)	$ (65,165)
Unrealized gains (losses) on debt securities, net of tax	8,393	(15,756)
Currency translation adjustment	104	(154)
Comprehensive loss	$ (115,826)	$ (81,075)

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(In thousands)
(Unaudited)

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity
Balance at December 31, 2021	141,210	$ 141	$ 1,964,167	$ (32,668)	$ (1,159,903)	$ 771,737
Net loss	—	—	—	—	(65,165)	(65,165)
Change in unrealized losses, net of tax	—	—	—	(15,756)	—	(15,756)
Foreign currency translation	—	—	—	(154)	—	(154)
Issuance of common stock in connection with employee stock plans	847	1	1,848	—	—	1,849
Stock-based compensation expense	—	—	26,236	—	—	26,236
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(304)	—	(9,173)	—	—	(9,173)
Balance at March 31, 2022	141,753	$ 142	$ 1,983,078	$ (48,578)	$ (1,225,068)	$ 709,574
Balance at December 31, 2022	142,058	$ 142	$ 2,059,850	$ (57,480)	$ (1,429,625)	$ 572,887
Net loss	—	—	—	—	(124,323)	(124,323)
Change in unrealized gains, net of tax	—	—	—	8,393	—	8,393
Foreign currency translation	—	—	—	104	—	104
Issuance of common stock in connection with employee stock plans	965	1	2,560	—	—	2,561
Stock-based compensation expense	—	—	26,948	—	—	26,948
Balance at March 31, 2023	143,023	$ 143	$ 2,089,358	$ (48,983)	$ (1,553,948)	$ 486,570

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)
(Unaudited)

	Three Months Ended March 31,	
	2023	**2022**
Operating activities:		
Net loss	$ (124,323)	$ (65,165)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	2,604	3,701
Amortization of right-of-use operating lease assets	2,395	602
Amortization of other assets	607	592
Amortization of premium (discount) on investments, net	(5,042)	4,175
Amortization of debt issuance costs	1,486	1,343
Non-cash interest related to sale of future royalties	15,363	—
Stock-based compensation expense	26,948	26,236
Loss (gain) on investments	529	(10)
Non-cash losses related to disposal of property, plant and equipment	—	527
Non-cash losses related to other assets	445	110
Changes in operating assets and liabilities:		
Contracts receivable	11,624	35,774
Inventories	(167)	774
Other current and long-term assets	5,312	(7,222)
Income taxes payable	11,037	865
Accounts payable	(10,295)	2,878
Accrued compensation	(31,018)	(22,285)
Accrued liabilities and other current liabilities	(28,460)	10,473
Deferred contract revenue	(13,037)	(25,018)
Net cash used in operating activities	(133,992)	(31,650)
Investing activities:		
Purchases of short-term investments	(688,278)	(462,855)
Proceeds from sale of short-term investments	374,363	178,837
Purchases of property, plant and equipment	(10,472)	(2,705)
Acquisition of licenses and other assets, net	(1,253)	(826)
Net cash used in investing activities	(325,640)	(287,549)
Financing activities:		
Proceeds from equity, net	2,560	1,848
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	—	(9,173)
Proceeds from sale of future royalties	500,000	—
Payments of transaction costs related to sale of future royalties	(10,434)	—
Principal payments on mortgage debt	(39)	—
Net cash provided by (used in) financing activities	492,087	(7,325)
Effects of exchange rates on cash	104	(154)
Net increase (decrease) in cash and cash equivalents	32,559	(326,678)
Cash and cash equivalents at beginning of period	276,472	869,191
Cash and cash equivalents at end of period	$ 309,031	$ 542,513
Supplemental disclosures of cash flow information:		
Interest paid	$ 89	$ 594
Income taxes paid	$ 293	$ 2
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 3,058	$ 1,344

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
March 31, 2023
(Unaudited)

1. Organization and Basis of Presentation

Organization and Business Activity

We incorporated in California on January 10, 1989. In conjunction with our initial public offering, we reorganized as a Delaware corporation in April 1991. We are a leader in the discovery and development of RNA-targeted therapeutics.

Basis of Presentation

We prepared the unaudited interim condensed consolidated financial statements for the three months ended March 31, 2023 and 2022 on the same basis as the audited financial statements for the year ended December 31, 2022. We included all normal recurring adjustments in the financial statements, which we considered necessary for a fair presentation of our financial position at such dates and our operating results and cash flows for those periods. Our operating results for the interim periods may not be indicative of what our operating results will be for the entire year. For more complete financial information, these financial statements, and notes thereto, should be read in conjunction with the audited financial statements for the year ended December 31, 2022 included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission, or SEC.

In our condensed consolidated financial statements, we included the accounts of Ionis Pharmaceuticals, Inc. and the consolidated results of our wholly owned subsidiary, Akcea Therapeutics, Inc. and its wholly owned subsidiaries (“we”, “us” or “our”).

We operate as a single segment, Ionis operations, because our chief decision maker reviews operating results on an aggregate basis and manages our operations as a single operating segment.

Use of Estimates

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States, or U.S., that require us to make estimates and assumptions that affect the amounts reported in our condensed consolidated financial statements and accompanying notes. Actual results could differ from our estimates.

2. Significant Accounting Policies

Our significant accounting policies have not changed substantially from those included in our Annual Report on Form 10-K for the year ended December 31, 2022, other than as discussed below.

Liability Related to Sale of Future Royalties

In January 2023, we entered into a royalty purchase agreement with Royalty Pharma Investments, or Royalty Pharma, to monetize a portion of our future SPINRAZA and pelacarsen royalties we are entitled to under our arrangements with Biogen and Novartis, respectively. Refer to Note 10, *Liability Related to Sale of Future Royalties*, for further details on the agreement.

We record upfront payments and milestone payments we receive from the sale of future royalties as a liability, net of transaction costs. We record royalty payments made to Royalty Pharma as a reduction of the liability and amortize the transaction costs over the estimated life of the related royalty stream. We account for the associated interest expense under the effective interest rate method, while continuing to recognize the full amount of royalty revenue in the period in which the counterparty sells the related product and recognizes the related revenue.

The liability related to the sale of future royalties, effective interest rate and the related interest expense are calculated using our current estimate of anticipated future royalty payments under the arrangement, which we periodically reassess based on internal projections and information from our partners who are responsible for commercializing the medicines. If there is a material change in our estimate, we will prospectively adjust the liability related to the sale of future royalties, effective interest rate and the related interest expense.

Recently Adopted Accounting Standards

We do not expect any recently issued accounting standards to have a material impact to our financial results.

3. Supplemental Financial Data

Inventories

Our inventory consisted of the following (in thousands):

	March 31, 2023	December 31, 2022
Raw materials:		
Raw materials - clinical	$ 17,356	$ 17,061
Raw materials - commercial	2,786	2,699
Total raw materials	20,142	19,760
Work in process	1,840	2,109
Finished goods	218	164
Total inventory	$ 22,200	$ 22,033

Accrued Liabilities

Our accrued liabilities consisted of the following (in thousands):

	March 31, 2023	December 31, 2022
Clinical development expenses	$ 85,694	$ 116,460
In-licensing expenses	12,704	7,945
Commercial expenses	4,704	3,498
Other miscellaneous expenses	9,600	12,198
Total accrued liabilities	$ 112,702	$ 140,101

4. Collaborative Arrangements and Licensing Agreements

Below, we have included our Biogen and GSK collaborations, which are our only collaborations with substantive changes during 2023 from those included in Part IV, Item 15, Note 7 of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2022.

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with spinal muscular atrophy, or SMA. Under our 2013 strategic neurology collaboration, Biogen developed QALSODY (tofersen), our recently approved medicine to treat people with superoxide dismutase 1 amyotrophic lateral sclerosis, or SOD1-ALS. We and Biogen are currently developing numerous investigational medicines to treat neurodegenerative diseases under these collaborations, including medicines in development to treat people with amyotrophic lateral sclerosis, or ALS, SMA, Angelman Syndrome, Alzheimer’s disease and Parkinson’s disease. In addition to these medicines, our collaborations with Biogen include a substantial research pipeline that addresses a broad range of neurological diseases. From inception through March 31, 2023, we have received more than $3.5 billion in payments from our Biogen collaborations.

In the first quarter of 2023, we earned a $10 million milestone payment from Biogen when we advanced ION582 under our 2012 neurology collaboration. We will recognize revenue as we perform services based on our effort to satisfy our research and development, or R&D, services performance obligation relative to the total effort expected to satisfy our performance obligation for ION582. We will achieve the next payment of up to $25 million if Biogen advances another medicine under our 2012 neurology collaboration.

During the three months ended March 31, 2023 and 2022, we earned the following revenue from our relationship with Biogen (in thousands, except percentage amounts):

	Three Months Ended March 31,	
	2023	2022
SPINRAZA royalties (commercial revenue)	$ 50,247	$ 53,818
R&D revenue	20,254	40,049
Total revenue from our relationship with Biogen	$ 70,501	$ 93,867
Percentage of total revenue	54%	66%

In April 2023, we earned a $16 million milestone payment from Biogen when the FDA approved Biogen's New Drug Application, or NDA, for QALSODY. We will achieve the next payment of up to $20 million if Biogen advances a medicine under the 2013 strategic neurology collaboration.

Our condensed consolidated balance sheets at March 31, 2023 and December 31, 2022 included deferred revenue of $340.9 million and $351.2 million, respectively, from our relationship with Biogen.

GSK

In March 2010, we entered into a collaboration with GSK using our antisense drug discovery platform to discover and develop new medicines against targets for serious and rare diseases, including infectious diseases and some conditions causing blindness. Our collaboration with GSK currently includes bepirovirsen, our medicine in development targeting hepatitis B virus, or HBV. We designed this medicine to reduce the production of viral proteins associated with HBV infection. In the third quarter of 2019, following positive Phase 2 results, GSK licensed our HBV program. GSK is responsible for all global development, regulatory and commercialization activities and costs for the HBV program. From inception through March 31, 2023, we have received more than $105 million in an upfront payment and payments related to the HBV program.

In the first quarter of 2023, we earned a $15 million milestone payment when GSK initiated a Phase 3 program of bepirovirsen. We recognized this milestone payment as R&D revenue in full in the first quarter of 2023 because we did not have any remaining performance obligations related to the milestone payment. We will achieve the next payment of $15 million if the FDA accepts an NDA filing of bepirovirsen for review.

During the three months ended March 31, 2023 and 2022, we earned the following revenue from our relationship with GSK (in thousands, except percentage amounts):

	Three Months Ended March 31,	
	2023	2022
R&D revenue	$ 15,000	$ —
Percentage of total revenue	11%	—

We did not have any deferred revenue from our relationship with GSK at March 31, 2023 or December 31, 2022.

5. Basic and Diluted Net Loss Per Share

Basic net loss per share

We calculated our basic net loss per share for the three months ended March 31, 2023 and 2022 by dividing our net loss by our weighted-average number of common shares outstanding during the period.

Diluted net loss per share

For the three months ended March 31, 2023 and 2022, we incurred a net loss; therefore, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock from the following would have had an anti-dilutive effect on net loss per share:

- 0 percent convertible senior notes, or 0% Notes;
- Note hedges related to the 0% Notes;
- 0.125 percent convertible senior notes, or 0.125% Notes;
- Note hedges related to the 0.125% Notes;
- Dilutive stock options;
- Unvested restricted stock units, or RSUs;
- Unvested performance restricted stock units, or PRSUs; and
- Employee Stock Purchase Plan, or ESPP.

Additionally as of March 31, 2023, we had warrants related to our 0% and 0.125% Notes outstanding. We will include the shares issuable under these warrants in our calculation of diluted earnings per share when the average market price per share of our common stock for the reporting period exceeds the strike price of the warrants.

6. Investments

The following table summarizes the contract maturity of the available-for-sale securities we held as of March 31, 2023:

One year or less	74%
After one year but within two years	23%
After two years but within three and a half years	3%
Total	100%

As illustrated above, at March 31, 2023, 97 percent of our available-for-sale securities had a maturity of less than two years.

All of our available-for-sale debt securities are available to us for use in our current operations. As a result, we categorize all of these securities as current assets even though the stated maturity of some individual securities may be one year or more beyond the balance sheet date.

We invest in available-for-sale securities with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Standard & Poor’s, Moody’s or Fitch, respectively.

At March 31, 2023, we had an equity ownership interest of less than 20 percent in seven private companies and three public companies with which we conduct business.

The following is a summary of our investments (in thousands):

March 31, 2023	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale debt securities:				
Corporate debt securities (1)	$ 623,940	$ 62	$ (6,026)	$ 617,976
Debt securities issued by U.S. government agencies	247,629	69	(1,283)	246,415
Debt securities issued by the U.S. Treasury (1)	556,394	62	(3,738)	552,718
Debt securities issued by states of the U.S. and political subdivisions of the states	57,322	4	(498)	56,828
Total debt securities with a maturity of one year or less	1,485,285	197	(11,545)	1,473,937
Corporate debt securities	200,661	336	(5,205)	195,792
Debt securities issued by U.S. government agencies	99,635	256	(649)	99,242
Debt securities issued by the U.S. Treasury	257,651	364	(2,726)	255,289
Debt securities issued by states of the U.S. and political subdivisions of the states	14,564	106	(182)	14,488
Total debt securities with a maturity of more than one year	572,511	1,062	(8,762)	564,811
Total available-for-sale debt securities	$ 2,057,796	$ 1,259	$ (20,307)	$ 2,038,748
Equity securities:				
Publicly traded equity securities included in other current assets (2)	$ 11,897	$ —	$ (4,508)	$ 7,389
Privately held equity securities included in deposits and other assets (3)	23,115	25,001	(5,125)	42,991
Total equity securities	35,012	25,001	(9,633)	50,380
Total available-for-sale debt and equity securities	$ 2,092,808	$ 26,260	$ (29,940)	$ 2,089,128

December 31, 2022	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale debt securities:				
Corporate debt securities (1)	$ 513,790	$ 23	$ (4,365)	$ 509,448
Debt securities issued by U.S. government agencies	133,585	—	(1,829)	131,756
Debt securities issued by the U.S. Treasury (1)	512,655	23	(5,124)	507,554
Debt securities issued by states of the U.S. and political subdivisions of the states	57,484	18	(686)	56,816
Other municipal debt securities	6,008	—	(14)	5,994
Total debt securities with a maturity of one year or less	1,223,522	64	(12,018)	1,211,568
Corporate debt securities	227,631	14	(10,143)	217,502
Debt securities issued by U.S. government agencies	34,339	—	(1,040)	33,299
Debt securities issued by the U.S. Treasury	245,030	—	(4,109)	240,921
Debt securities issued by states of the U.S. and political subdivisions of the states	18,314	116	(329)	18,101
Total debt securities with a maturity of more than one year	525,314	130	(15,621)	509,823
Total available-for-sale debt securities	$ 1,748,836	$ 194	$ (27,639)	$ 1,721,391
Equity securities:				
Publicly traded equity securities included in other current assets (2)	$ 11,897	$ —	$ (1,358)	$ 10,539
Privately held equity securities included in deposits and other assets (3)	23,115	17,257	—	40,372
Total equity securities	35,012	17,257	(1,358)	50,911
Total available-for-sale debt and equity securities	$ 1,783,848	$ 17,451	$ (28,997)	$ 1,772,302

(1) Includes investments classified as cash equivalents in our condensed consolidated balance sheets.

(2) Our publicly traded equity securities are included in other current assets. We recognize publicly traded equity securities at fair value. In the three months ended March 31, 2023, we recognized a $3.2 million unrealized loss in our condensed consolidated statements of operations related to a decrease in the fair value of our investments in publicly traded companies.

(3) Our privately held equity securities are included in deposits and other assets. We recognize our privately held equity securities at cost minus impairments, plus or minus changes resulting from observable price changes in orderly transactions for the identical or similar investment of the same issuer, which are Level 3 inputs. In the three months ended March 31, 2023, we recorded a net gain of $2.6 million in our condensed consolidated statements of operations related to changes in the fair value of our investments in privately held companies.

The following is a summary of our investments we consider to be temporarily impaired at March 31, 2023 (in thousands, except for number of investments):

		Less than 12 Months of Temporary Impairment		More than 12 Months of Temporary Impairment		Total Temporary Impairment	
	Number of Investments	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	361	$ 434,500	$ (1,697)	$ 291,713	$ (9,534)	$ 726,213	$ (11,231)
Debt securities issued by U.S. government agencies	68	138,211	(424)	70,965	(1,508)	209,176	(1,932)
Debt securities issued by the U.S. Treasury	64	603,444	(3,873)	91,448	(2,591)	694,892	(6,464)
Debt securities issued by states of the U.S. and political subdivisions of the states	110	22,778	(140)	32,792	(540)	55,570	(680)
Total temporarily impaired securities	603	$ 1,198,933	$ (6,134)	$ 486,918	$ (14,173)	$ 1,685,851	$ (20,307)

We believe that the decline in value of these securities is temporary and is primarily related to the change in market interest rates since purchase rather than underlying credit deterioration for any of the issuers. We believe it is more likely than not that we will be able to hold our debt securities with declines in value to maturity. Therefore, we anticipate full recovery of our debt securities' amortized cost basis at maturity.

7. Fair Value Measurements

The following tables present the major security types we held at March 31, 2023 and December 31, 2022 that we regularly measure and carry at fair value. The following tables segregate each security type by the level within the fair value hierarchy of the valuation techniques we utilized to determine the respective security's fair value (in thousands):

	At March 31, 2023	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 276,352	$ 276,352	$ —
Corporate debt securities (2)	813,768	—	813,768
Debt securities issued by U.S. government agencies (2)	345,657	—	345,657
Debt securities issued by the U.S. Treasury (2)	808,007	808,007	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	71,316	—	71,316
Publicly traded equity securities included in other current assets (4)	7,389	7,389	—
Total	$ 2,322,489	$ 1,091,748	$ 1,230,741

	At December 31, 2022	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 211,655	$ 211,655	$ —
Corporate debt securities (5)	726,950	—	726,950
Debt securities issued by U.S. government agencies (2)	165,055	—	165,055
Debt securities issued by the U.S. Treasury (2)	748,475	748,475	—
Debt securities issued by states of the U.S. and political subdivisions of the states (2)	74,917	—	74,917
Other municipal debt securities (2)	5,994	—	5,994
Publicly traded equity securities included in other current assets (4)	10,539	10,539	—
Total	$ 1,943,585	$ 970,669	$ 972,916

The following footnotes reference lines in our condensed consolidated balance sheets:

(1) Included in cash and cash equivalents in our condensed consolidated balance sheets.

(2) Included in short-term investments in our condensed consolidated balance sheets.

(3) $1.0 million was included in cash and cash equivalents in our condensed consolidated balance sheets, with the difference included in short-term investments in our condensed consolidated balance sheets.

(4) Included in other current assets in our condensed consolidated balance sheets.

(5) $11.0 million was included in cash and cash equivalents in our condensed consolidated balance sheets, with the difference included in short-term investments in our condensed consolidated balance sheets.

Convertible Notes

Our 0.125% Notes and 0% Notes had a fair value of $506.3 million and $578.4 million at March 31, 2023, respectively. Our 0.125% Notes and 0% Notes had a fair value of $498.9 million and $587.3 million at December 31, 2022, respectively. We determine the fair value of our notes based on quoted market prices for these notes, which are Level 2 measurements because the notes do not trade regularly.

8. Stock-based Compensation Expense

We measure stock-based compensation expense for equity-classified awards, principally related to stock options, RSUs, PRSUs and stock purchase rights under our ESPP based on the estimated fair value of the award on the date of grant. We recognize the value of the portion of the award that we ultimately expect to vest as stock-based compensation expense over the requisite service period in our condensed consolidated statements of operations. We reduce stock-based compensation expense for estimated forfeitures at the time of grant and revise in subsequent periods if actual forfeitures differ from those estimates. We use the Black-Scholes model to estimate the fair value of stock options granted and stock purchase rights under our ESPP.

On the grant date, we use our stock price and assumptions regarding a number of variables to determine the estimated fair value of stock-based payment awards. These variables include, but are not limited to, our expected stock price volatility over the term of the awards, and actual and projected employee stock option exercise behaviors.

We recognize compensation expense for stock options granted, RSUs, PRSUs and stock purchase rights under the ESPP using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), we recognize compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period.

For the three months ended March 31, 2023 and 2022, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Three Months Ended March 31,	
	2023	2022
Risk-free interest rate	3.6%	1.7%
Dividend yield	0.0%	0.0%
Volatility	47.5%	55.2%
Expected life*	6.3 years	6.3 years

* In 2021, our Compensation Committee approved an amendment to the 2011 Equity Incentive Plan, or 2011 Plan, and the 2020 Equity Incentive Plan, or 2020 Plan, that increased the contractual term of stock options granted under these plans from seven years to ten years for stock options granted on January 1, 2022 and thereafter. We determined that we are unable to rely on our historical exercise data as a basis for estimating the expected life of stock options granted to employees following this change because the contractual term changed and we have no other means to reasonably estimate future exercise behavior. We therefore used the simplified method for determining the expected life of stock options granted to employees in the three months ended March 31, 2023 and 2022. Under the simplified method, we calculate the expected term as the average of the time-to-vesting and the contractual life of the options. As we gain additional historical information, we will transition to calculating our expected term based on our historical exercise patterns.

ESPP:

	Three Months Ended March 31,	
	2023	2022
Risk-free interest rate	5.2%	0.6%
Dividend yield	0.0%	0.0%
Volatility	36.7%	50.2%
Expected life	6 months	6 months

RSUs:

The fair value of RSUs is based on the market price of our common stock on the date of grant. The RSUs we have granted to employees vest annually over a four-year period. The RSUs we granted to our board of directors prior to June 2020 vest annually over a four-year period. The RSUs we granted after June 2020 to our board of directors fully vest after one year. The weighted-average grant date fair value of RSUs granted to employees for the three months ended March 31, 2023 was $39.85 per share.

PRSUs:

Beginning in 2020, we added PRSU awards to the compensation for our Chief Executive Officer, Dr. Brett Monia. In 2022, we added PRSU awards to the compensation for our other Section 16 officers. Beginning in 2023, we added PRSU awards to the compensation for all executive officers.

Under the terms of the PRSUs we granted in 2020 through 2022, one third of the PRSUs may vest at the end of three separate performance periods spread over the three years following the date of grant (i.e., the one-year period commencing on the date of grant and ending on the first anniversary of the date of grant, the two-year period commencing on the date of grant and ending on the second anniversary of the date of grant and the three-year period commencing on the date of grant and ending on the third anniversary of the date of grant) based on our relative total shareholder return, or TSR, as compared to a peer group of companies, and as measured, in each case, at the end of the applicable performance period. Under the terms of the grants, no number of PRSUs is guaranteed to vest and the actual number of PRSUs that will vest at the end of each performance period may be anywhere from zero percentto 150 percent of the target number depending on our relative TSR.

Under the terms of the PRSUs we granted in 2023, 100 percent of the PRSUs may vest at the end of the three-year performance period based on our relative TSR as compared to a peer group of companies and as measured at the end of the performance period. Under the terms of the grants, no number of PRSUs is guaranteed to vest and the actual number of PRSUs that will vest at the end of each performance period may be anywhere from zero to 200 percent of the target number depending on our relative TSR.

We determined the fair value of the PRSUs using a Monte Carlo model because the performance target is based on our relative TSR, which represents a market condition. The weighted-average grant date fair value of PRSUs granted to our executive officers for the three months ended March 31, 2023 and 2022 were $58.99 and $42.28 per share, respectively.

The following table summarizes stock-based compensation expense for the three months ended March 31, 2023 and 2022 (in thousands):

	Three Months Ended March 31,	
	2023	2022
Cost of sales	$ 119	$ 160
Research, development and patent expense	19,567	19,082
Selling, general and administrative expense	7,262	6,994
Total	$ 26,948	$ 26,236

As of March 31, 2023, total unrecognized estimated stock-based compensation expense related to non-vested stock options, RSUs and PRSUs was $60.2 million, $79.1 million and $9.5 million, respectively. Our actual expenses may differ from these estimates because we will adjust our unrecognized stock-based compensation expense for future forfeitures, including any PRSUs that do not vest. We expect to recognize the cost of stock-based compensation expense related to our non-vested stock options, RSUs and PRSUs over a weighted average amortization period of 1.4 years, 1.8 years and 2.2 years, respectively.

9. Income Taxes

Beginning in 2022, the Tax Cuts and Jobs Act of 2017, or TCJA, requires taxpayers to amortize research and development expenditures over five years pursuant to Internal Revenue Code, or IRC, Section 174. Additionally, we expect to reflect the royalty purchase agreement with Royalty Pharma as a taxable sale, requiring us to include the proceeds from the sale, net of currently deductible issuance costs, as taxable income in 2023.

We recorded income tax expense of $11.4 million and $1.1 million for the three months ended March 31, 2023 and 2022, respectively. The increase in income tax expense for the three months ended March 31, 2023, compared to the same period in 2022, relates primarily to the impact of the Royalty Pharma transaction.

10. Liability Related to Sale of Future Royalties

In January 2023, we entered into a royalty purchase agreement with Royalty Pharma to monetize a portion of our future SPINRAZA and pelacarsen royalties we are entitled to under our arrangements with Biogen and Novartis, respectively. As a result, we received an upfront payment of $500 million and we are eligible to receive up to $625 million in additional milestone payments. Under the terms of the agreement, Royalty Pharma will receive 25 percent of our SPINRAZA royalty payments from 2023 through 2027, increasing to 45 percent of royalty payments in 2028, on up to $1.5 billion in annual sales. In addition, Royalty Pharma will receive 25 percent of any future royalty payments on pelacarsen, our medicine in development to treat patients with elevated lipoprotein(a), or Lp(a), and cardiovascular disease. Royalty Pharma’s royalty interest in SPINRAZA will revert to us after total SPINRAZA royalty payments to Royalty Pharma reach either $475 million or $550 million, depending on the timing and occurrence of FDA approval of pelacarsen.

We recorded the upfront payment of $500 million as a liability related to the sale of future royalties, net of transaction costs of $10.4 million, which we are amortizing over the estimated life of the arrangement using the effective interest rate method. We recognize royalty revenue in the period in which the counterparty sells the related product and recognizes the related revenue. We record royalty payments made to Royalty Pharma as a reduction of the liability.

We estimate the effective interest rate used to record interest expense under this agreement based on the estimate of future royalty payments to Royalty Pharma. As of March 31, 2023, the estimated effective interest rate under the agreement was 13.5 percent.

The following is a summary of our liability related to sale of future royalties for the three months ended March 31, 2023 (in thousands):

Proceeds from sale of future royalties	$	500,000
Interest expense related to sale of future royalties		15,363
Liability related to sale of future royalties as of March 31, 2023	$	515,363
Net issuance costs related to sale of future royalties as of March 31, 2023		(10,282)
Net liability related to sale of future royalties as of March 31, 2023	$	505,081

There are numerous factors, most of which are not within our control, that could materially impact the amount and timing of royalty payments from Biogen and Novartis, and result in changes to our estimate of future royalty payments to Royalty Pharma. Such factors include, but are not limited to the commercial sales of SPINRAZA, the regulatory approval and commercial sales of pelacarsen, competing products or other significant events.

11. Convertible Debt

0 Percent Convertible Senior Notes and Call Spread

In April 2021, we completed a $632.5 million offering of convertible senior notes. We used a portion of the net proceeds from the issuance of the 0% Notes to repurchase $247.9 million in principal of our 1% Notes for $257.0 million.

At March 31, 2023, we had the following 0% Notes outstanding (in millions except interest rate and price per share data):

		0% Notes
Outstanding principal balance	$	632.5
Unamortized debt issuance costs	$	9.5
Maturity date		April 2026
Interest rate		0 percent
Effective interest rate		0.5 percent
Conversion price per share	$	57.84
Effective conversion price per share with call spread	$	76.39
Total shares of common stock subject to conversion		10.9

In conjunction with the April 2021 offering, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants, to minimize the impact of potential economic dilution upon conversion of our 0% Notes by increasing the effective conversion price on our 0% Notes. We increased our effective conversion price to $76.39 with the same number of underlying shares as our 0% Notes. The call spread cost us $46.9 million, of which $136.7 million was for the note hedge purchase, offset by $89.8 million we received for selling the warrants. Similar to our 0% Notes, our note hedges are subject to adjustment. Additionally, our note hedges are exercisable upon conversion of the 0% Notes. The note hedges will expire upon maturity of the 0% Notes, or April 2026. The note hedges and warrants are separate transactions and are not part of the terms of our 0% Notes. The holders of the 0% Notes do not have any rights with respect to the note hedges and warrants.

We recorded the amount we paid for the note hedges and the amount we received for the warrants in additional paid-in capital in our condensed consolidated balance sheets. Refer to Part IV, Item 15, Note 1 of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2022 for our Call Spread accounting policy. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

0.125 Percent Convertible Senior Notes and Call Spread

At March 31, 2023, we had the following 0.125% Notes outstanding with interest payable semi-annually (in millions except interest rate and price per share data):

	0.125% Notes
Outstanding principal balance	$ 548.8
Unamortized debt issuance costs	$ 3.8
Maturity date	December 2024
Interest rate	0.125 percent
Effective interest rate	0.5 percent
Conversion price per share	$ 83.28
Effective conversion price per share with call spread	$ 123.38
Total shares of common stock subject to conversion	6.6

In conjunction with the issuance of our 0.125% Notes in December 2019, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants, to minimize the impact of potential economic dilution upon conversion of our 0.125% Notes by increasing the effective conversion price on our 0.125% Notes. We increased our effective conversion price to $123.38 with the same number of underlying shares as our 0.125% Notes. The call spread cost us $52.6 million, of which $108.7 million was for the note hedge purchase, offset by $56.1 million we received for selling the warrants. Similar to our 0.125% Notes, our note hedges are subject to adjustment. Additionally, our note hedges are exercisable upon conversion of the 0.125% Notes. The note hedges will expire upon maturity of the 0.125% Notes, or December 2024. The note hedges and warrants are separate transactions and are not part of the terms of our 0.125% Notes. The holders of the 0.125% Notes do not have any rights with respect to the note hedges and warrants.

We recorded the amount we paid for the note hedges and the amount we received for the warrants in additional paid-in capital in our condensed consolidated balance sheets. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

Other Terms of Convertible Senior Notes

The 0% and 0.125% Notes are convertible under certain conditions, at the option of the note holders. We can settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both. We may not redeem the notes prior to maturity, and we do not have to provide a sinking fund for them. Holders of the notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indentures governing the notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus any accrued and unpaid interest.

12. Legal Proceedings

From time to time, we are involved in legal proceedings arising in the ordinary course of our business. Periodically, we evaluate the status of each legal matter and assess our potential financial exposure. If we consider the potential loss from any legal proceeding to be probable and we can reasonably estimate the amount, we accrue a liability for the estimated loss. The outcome of any proceeding is not determinable in advance. Therefore, we are required to use significant judgment to determine the probability of a loss and whether the amount of the loss is reasonably estimable. Our assessment of a potential liability and the amount of accruals we recorded are based only on the information available to us at the time. As additional information becomes available, we reassess the potential liability related to the legal proceeding and may revise our estimates.

On January 19, 2022, a purported stockholder of Ionis filed a stockholder derivative complaint in the Delaware Court of Chancery captioned Leo Shumacher, et al. v. Joseph Loscalzo, et al., C.A. No. 2022-0059, or the Shumacher Action. The complaint names Ionis' board of directors, or the Board, as defendants and names Ionis as a nominal defendant. The Shumacher Action Plaintiff asserts a breach of fiduciary duty claim against the Board for awarding and receiving allegedly excessive compensation. The Shumacher Action Plaintiff also asserts an unjust enrichment claim against the non-executive directors as a result of the compensation they received. The complaint seeks, among other things, damages, restitution, attorneys' fees and costs, and such other relief as deemed just and proper by the court. On March 18, 2022, Ionis and the Board moved to dismiss the complaint. On May 24, 2022, the parties entered into a Stipulation and Agreement of Compromise, Settlement and Release.

On May 25, 2022, another purported stockholder of Ionis filed a stockholder derivative complaint also in the Delaware Court of Chancery captioned Robert S. Cohen, et al. v. Joseph Loscalzo, et al., C.A. No. 2022-0453, or the Cohen Action. The complaint names the Board as defendants and names Ionis as a nominal defendant. The Cohen Action Plaintiff asserts claims for breach of fiduciary duty, unjust enrichment, aiding and abetting breaches of fiduciary duty, and waste against the Board for awarding and receiving allegedly excessive non-executive director compensation for the years 2018, 2019, and 2020. On June 2, 2022, the Cohen Action Plaintiff filed a motion to consolidate the related Cohen Action and Shumacher Action. On July 5, 2022, the Court denied the motion to consolidate in favor of the settlement pending in the Shumacher Action.

On July 18, 2022, Ionis filed a Form 8-K disclosing the pending settlement and attaching the Notice of Pendency of Settlement of Action. On September 21, 2022, the Court held a hearing to consider whether the terms of the settlement should be approved, at which hearing the Cohen Action plaintiff objected to the settlement. At the conclusion of the hearing, the Court declined to approve the settlement and directed the parties to meet and confer on the issue of the scope of the release. On February 7, 2023, the parties entered into an Amended Stipulation and Agreement of Compromise, Settlement and Release, which folded the Cohen Action into the settlement, or the Revised Settlement. The settlement did not have a material impact on our condensed consolidated financial statements. On April 24, 2023, the Court issued an Order and Final Judgment approving the Revised Settlement and dismissing the Shumacher and Cohen Actions, and all claims contained therein, with prejudice. The Order does not contain any admission of wrongdoing by any defendant.

ITEM 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

In this Report on Form 10-Q, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us," means Ionis Pharmaceuticals, Inc. and its wholly owned affiliate, Akcea Therapeutics, Inc.

Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, the Report includes forward-looking statements regarding our business and the therapeutic and commercial potential of QALSODY (tofersen), SPINRAZA (nusinersen), TEGSEDI (inotersen), WAYLIVRA (volanesorsen), eplontersen, olezarsen, donidalorsen, ION363, pelacarsen, bepirovirsen, our technologies and our other products in development. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this report and described in additional detail in our annual report on Form 10-K for the year ended December 31, 2022, which is on file with the U.S. Securities and Exchange Commission and is available from us, and those identified within Part II Item 1A. Risk Factors of this Report. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements.

Overview

We were founded over 30 years ago to deliver innovative medicines for diseases with great medical need. Today, we are building on our advancements in RNA-targeted therapeutics to move us closer to achieving our vision to be the leader in genetic medicines. We believe our medicines have the potential to pioneer new markets, change standards of care and transform the lives of people with devastating diseases. We currently have four marketed medicines: QALSODY, SPINRAZA, TEGSEDI and WAYLIVRA. On April 25, 2023, the U.S. Food and Drug Administration, or FDA, granted Biogen accelerated approval of QALSODY for the treatment of superoxide dismutase 1 amyotrophic lateral sclerosis, or SOD1-ALS. Additionally, the FDA accepted our New Drug Application, or NDA, of eplontersen for polyneuropathy caused by hereditary TTR amyloidosis, or ATTRv-PN. Eplontersen's Prescription Drug User Fee Act, or PDUFA, date is December 22, 2023. We also have a rich innovative late- and mid-stage pipeline primarily focused on our leading cardiovascular and neurology franchises. We recently expanded our Phase 3 pipeline to seven programs across nine indications following the start of GSK's bepirovirsen hepatitis B program.

Our multiple sources of revenue and strong balance sheet enable us to continue investing in our commercial readiness efforts for multiple late-stage programs and our innovative pipeline. By continuing to focus on these priorities, we believe we are well positioned to drive future growth and to deliver increasing value for patients and shareholders.

Marketed Medicines

SPINRAZA is the global market leader for the treatment of patients with spinal muscular atrophy, or SMA, a progressive, debilitating and often fatal genetic disease. Biogen is our partner responsible for commercializing SPINRAZA worldwide. From inception through March 31, 2023, we have earned more than $1.9 billion in revenues from our SPINRAZA collaboration, including more than $1.4 billion in royalties on sales of SPINRAZA.

TEGSEDI is a once weekly, self-administered subcutaneous medicine approved in the U.S., Europe, Canada and Brazil for the treatment of patients with polyneuropathy caused by hereditary polyneuropathy, or ATTRv-PN, a debilitating, progressive, and fatal disease. We launched TEGSEDI in the United States, or U.S., and the European Union, or EU, in late 2018. In 2021, we began selling TEGSEDI in Europe through our distribution agreement with Swedish Orphan Biovitrum AB, or Sobi, and in the second quarter of 2021, Sobi began distributing TEGSEDI in the U.S. and Canada. In Latin America, PTC Therapeutics International Limited, or PTC, is commercializing TEGSEDI in Brazil and is pursuing access in additional Latin American countries through its exclusive license agreement with us.

WAYLIVRA is a once weekly, self-administered, subcutaneous medicine that received conditional marketing authorization in May 2019 from the European Commission, or EC, as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, and at high risk for pancreatitis. We launched WAYLIVRA in the EU in the third quarter of 2019. In 2021, we began selling WAYLIVRA in Europe through our distribution agreement with Sobi. In Latin America, PTC is commercializing WAYLIVRA in Brazil for two indications, FCS and familial partial lipodystrophy, or FPL, and is pursuing access in additional Latin American countries through its exclusive license agreement with us.

QALSODY is an antisense medicine that received accelerated approval in April 2023 from the FDA for the treatment of patients with SOD1-ALS, a rare, neurodegenerative disorder that causes progressive loss of motor neurons leading to death. The European Medicines Agency, or EMA, is currently reviewing QALSODY for approval in the EU.

Medicines in Registration and Phase 3 Studies

We currently have seven medicines in Phase 3 studies for nine indications, which include:

- Eplontersen: our medicine in development for transthyretin amyloidosis, or ATTR
  - We are currently conducting the Phase 3 NEURO-TTRansform study in patients with ATTRv-PN, the Phase 3 CARDIO-TTRansform study in patients with ATTR cardiomyopathy, or ATTR-CM, and additional studies supporting our ATTR development program
    - In March 2023, the FDA accepted the NDA for eplontersen in the U.S. for patients with ATTRv-PN with a PDUFA date of December 22, 2023
    - In April 2023, we presented positive week-35 and week-66 data from the Phase 3 NEURO-TTRansform study in patients with ATTRv-PN at the American Academy of Neurology Annual Meeting
- Olezarsen: our medicine in development for FCS and severe hypertriglyceridemia, or SHTG
  - We are currently conducting a broad Phase 3 development program for olezarsen that includes the Phase 3 BALANCE study in patients with FCS and three Phase 3 studies supporting development for the treatment of SHTG: CORE, CORE2 and ESSENCE
    - We remain on track for data from the Phase 3 BALANCE FCS study in the second half of 2023
    - The FDA granted olezarsen fast track designation for the treatment of patients with FCS
    - In the second half of 2022, we expanded our Phase 3 program for SHTG when we initiated CORE2, a confirmatory Phase 3 study of olezarsen in patients with SHTG and ESSENCE, a supporting Phase 3 study of olezarsen in patients with SHTG or hypertriglyceridemia and atherosclerotic cardiovascular disease
- Donidalorsen: our medicine in development for hereditary angioedema, or HAE
  - We are currently conducting the Phase 3 OASIS-HAE study in patients with HAE and the Phase 3 OASIS-Plus supportive study for HAE patients previously treated with other prophylactic therapies
    - We remain on track to complete enrollment in the Phase 3 OASIS-HAE study in mid-2023 with data expected in the first half of 2024
    - We reported positive data from the Phase 2 study and Phase 2 open-label extension, or OLE, study throughout 2022 and early 2023
- ION363: our medicine in development for amyotrophic lateral sclerosis, or ALS, with mutations in the fused in sarcoma gene, or FUS
  - We are currently conducting a Phase 3 study of ION363 in juvenile and adult patients with FUS-ALS
- QALSODY: our medicine in development for superoxide dismutase 1 ALS, or SOD1-ALS
  - Biogen is developing QALSODY, including conducting the ongoing Phase 3 ATLAS study in presymptomatic SOD1 patients
    - The FDA granted Biogen accelerated approval of QALSODY for patients with SOD1-ALS
    - The EMA is currently reviewing QALSODY's Marketing Authorization Application, or MAA, in the EU
    - In June 2022, Biogen presented new positive data from the ongoing VALOR OLE study at the European Network to Cure ALS, or ENCALS, meeting. These data were included in the NDA filing in the U.S. and MAA filing in the EU
- Pelacarsen: our medicine in development to treat patients with elevated lipoprotein(a), or Lp(a) and cardiovascular disease
  - Novartis is developing pelacarsen, including conducting the ongoing Lp(a) HORIZON Phase 3 cardiovascular outcome study in patients with established cardiovascular disease and elevated Lp(a)
    - In July 2022, Novartis achieved full enrollment in the Lp(a) HORIZON study
- Bepirovirsen: our medicine in development for hepatitis B virus, or HBV
  - GSK is developing bepirovirsen, including conducting the ongoing B-Well Phase 3 program in patients with HBV
    - In 2022, GSK presented positive data from the Phase 2b B-Clear study of bepirovirsen demonstrating potential for functional cures in patients with chronic HBV

Critical Accounting Estimates

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the U.S. As such, we make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management reviews the development, selection and disclosure of such estimates with the audit committee of our board of directors. The following are our significant accounting estimates, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results:

- Assessing the propriety of revenue recognition and associated deferred revenue; and
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities

There have been no other material changes to our critical accounting policies and estimates from the information provided in Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations" included in our Annual Report on Form 10-K for the year ended December 31, 2022.

Results of Operations

The following is a summary of our financial results (in millions):

	Three Months Ended March 31	
	2023	2022
Total revenue	$ 130.5	$ 141.9
Total operating expenses	$ 244.7	$ 199.4
Loss from operations	$ (114.1)	$ (57.5)
Net loss	$ (124.3)	$ (65.2)

Revenue

Total revenue for the three months ended March 31, 2023 was $130.5 million compared to $141.9 million for the same period in 2022 and was comprised of the following (in millions):

	Three Months Ended March 31,	
	2023	2022
Revenue:		
Commercial revenue:		
SPINRAZA royalties	$ 50.2	$ 53.8
TEGSEDI and WAYLIVRA revenue, net	6.5	6.2
Licensing and other royalty revenue	11.0	12.3
Total commercial revenue	67.7	72.3
R&D revenue:		
Amortization from upfront payments	15.6	17.4
Milestone payments	22.5	27.2
License fees	—	2.0
Other services	0.3	3.1
Collaborative agreement revenue	38.4	49.7
Eplontersen joint development revenue	24.4	19.9
Total R&D revenue	62.8	69.6
Total revenue	$ 130.5	$ 141.9

We continued to derive our revenue for the first quarter of 2023 from diverse sources, with approximately half of our revenue coming from commercial products and half from numerous partnered programs. Commercial revenue for the first quarter of 2023 included $50 million from SPINRAZA royalties. Global SPINRAZA product sales of $443 million decreased six percent in the first quarter of 2023 compared to the same period in 2022 primarily due to the impact from foreign currency, fewer new patient starts in the U.S. and channel dynamics.

R&D revenue for the first quarter of 2023 included $24 million from AstraZeneca for its share of the global Phase 3 development costs for eplontersen, $20 million from Biogen for advancing several neurology disease programs and $15 million from GSK for advancing bepirovirsen into Phase 3 development.

Already in the second quarter of 2023, we have earned a $16 million milestone payment when QALSODY was approved in the U.S.

Eplontersen Collaboration with AstraZeneca

Our financial results for the three months ended March 31, 2023 and 2022 reflected the cost-sharing provisions related to our collaboration with AstraZeneca to develop and commercialize eplontersen for the treatment of ATTR. Under the terms of the collaboration agreement, AstraZeneca is currently paying 55 percent of the costs associated with the ongoing global Phase 3 development program. Because we are leading and conducting the Phase 3 development program, we are recognizing as R&D revenue the 55 percent of cost-share funding AstraZeneca is responsible for, net of our share of AstraZeneca's development expenses, in the same period we incur the related development expenses. In the first quarter of 2023, we earned $24 million in joint development revenue and recorded $47 million of R&D expenses related to Phase 3 development expenses under this collaboration. In the first quarter of 2022, we earned $20 million in joint development revenue and recorded $36 million of R&D expenses related to Phase 3 development expenses under this collaboration.

As AstraZeneca is responsible for the majority of the medical affairs and commercial costs in the U.S. and all costs associated with bringing eplontersen to market outside the U.S., we are recognizing cost-share funding we receive from AstraZeneca related to these activities as a reduction of our medical affairs and commercialization expenses, which we classify as R&D and selling, general and administrative, or SG&A expenses, respectively. In the first quarter of 2023, we recognized $0.7 million and $1.3 million of medical affairs expenses and commercialization expenses for eplontersen, respectively, net of cost-share funding from AstraZeneca. In the first quarter of 2022, we recognized $0.4 million and $0.2 million of medical affairs expenses and commercialization expenses for eplontersen, respectively, net of cost-share funding from AstraZeneca. We expect our medical affairs and commercialization expenses to increase as eplontersen advances toward the market under our collaboration with AstraZeneca.

Operating Expenses

Our operating expenses were as follows (in millions):

	Three Months Ended March 31,	
	2023	**2022**
Operating expenses, excluding non-cash compensation expense related to equity awards	$ 217.7	$ 173.1
Non-cash compensation expense related to equity awards	27.0	26.3
Total operating expenses	$ 244.7	$ 199.4

Operating expenses, excluding non-cash compensation expense related to equity awards, for the three months ended March 31, 2023 increased compared to the same period in 2022. Our R&D expenses increased as we advanced our pipeline, which included an increase in the costs associated with our clinical studies as most of our Phase 3 studies were either fully enrolled or approaching full enrollment at the end of March 2023. Our SG&A expenses increased due to expenses related to our go-to-market activities for eplontersen, olezarsen and donidalorsen. We expect our operating expenses, excluding non-cash compensation expense related to equity awards, to continue to increase during the remainder of 2023 as we continue to advance our late-stage medicines in development and prepare for commercialization.

To analyze and compare our results of operations to other similar companies, we believe it is important to exclude non-cash compensation expense related to equity awards from our operating expenses. We believe non-cash compensation expense related to equity awards is not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding it.

Cost of Sales

Our cost of sales consisted of manufacturing costs, including certain fixed costs, transportation and freight, indirect overhead costs associated with the manufacturing and distribution of TEGSEDI and WAYLIVRA and certain associated period costs.

Our cost of sales were as follows (in millions):

	Three Months Ended March 31,	
	2023	**2022**
Cost of sales, excluding non-cash compensation expense related to equity awards	$ 1.2	$ 4.0
Non-cash compensation expense related to equity awards	0.1	0.2
Total cost of sales	$ 1.3	$ 4.2

Research, Development and Patent Expenses

Our research, development and patent expenses consist of expenses for drug discovery, drug development, manufacturing and development chemistry and R&D support expenses.

The following table sets forth information on research, development and patent expenses (in millions):

	Three Months Ended March 31,	
	2023	**2022**
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 178.2	$ 142.0
Non-cash compensation expense related to equity awards	19.6	19.1
Total research, development and patent expenses	$ 197.8	$ 161.1

Drug Discovery

We use our proprietary antisense technology to generate information about the function of genes and to determine the value of genes as drug discovery targets. We use this information to direct our own drug discovery research, and that of our partners. Drug discovery is also the function that is responsible for advancing our core technology. This function is also responsible for making investments in complementary technologies to expand the reach of our technologies.

Our drug discovery expenses were as follows (in millions):

	Three Months Ended March 31,	
	2023	**2022**
Drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 24.6	$ 19.1
Non-cash compensation expense related to equity awards	3.9	4.1
Total drug discovery expenses	$ 28.5	$ 23.2

Drug discovery expenses, excluding non-cash compensation expense related to equity awards, increased in the three months ended March 31, 2023 compared to the same period in 2022 as we continued to advance our research programs.

Drug Development

The following table sets forth drug development expenses, including expenses for our marketed medicines and those in Phase 3 development for which we have incurred significant costs (in millions):

	Three Months Ended March 31,	
	2023	2022
TEGSEDI and WAYLIVRA	$ —	$ 2.1
Eplontersen	37.0	27.0
Olezarsen	26.8	8.7
Donidalorsen	5.3	1.7
ION363	2.3	1.7
Other antisense development projects	19.1	29.5
Development overhead expenses	25.1	19.3
Total drug development expenses, excluding non-cash compensation expense related to equity awards	115.6	90.0
Non-cash compensation expense related to equity awards	8.8	8.6
Total drug development expenses	$ 124.4	$ 98.6

Our development expenses, excluding non-cash compensation expense related to equity awards, increased for the three months ended March 31, 2023 compared to the same period in 2022 primarily due to our advancing late-stage pipeline and full or nearly full enrollment of multiple Phase 3 studies.

We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials, we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are clinical research programs that fuel our Phase 3 pipeline. When our medicines are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state in which we may adjust the development strategy for each medicine. Although we may characterize a medicine as “in Phase 1” or “in Phase 2,” it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous medicines based on each medicine’s particular needs at that time. This means we are constantly shifting resources among medicines. Therefore, what we spend on each medicine during a particular period is usually a function of what is required to keep the medicines progressing in clinical development, not what medicines we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one medicine to another and cannot be used to accurately predict future costs for each medicine. Because we always have numerous medicines in preclinical and varying stages of clinical research, the fluctuations in expenses from medicine to medicine, in large part, offset one another. If we partner a medicine, it may affect the size of a trial, its timing, its total cost and the timing of the related costs.

Medical Affairs

Our medical affairs function is responsible for communicating scientific and clinical information to healthcare providers, medical professionals and patients.

Our medical affairs expenses were as follows (in millions):

	Three Months Ended March 31,	
	2023	2022
Medical affairs expenses, excluding non-cash compensation expense related to equity awards	$ 4.3	$ 2.8
Non-cash compensation expense related to equity awards	1.0	0.3
Total medical affairs expenses	$ 5.3	$ 3.1

Medical affairs expenses, excluding non-cash compensation expense related to equity awards, increased in the three months ended March 31, 2023 compared to the same period in 2022. We expect medical affairs expenses, excluding non-cash compensation expense related to equity awards, to increase in the remainder of 2023 as we advance our late-stage pipeline.

Manufacturing and Development Chemistry

Expenditures in our manufacturing and development chemistry function consist primarily of personnel costs, specialized chemicals for oligonucleotide manufacturing, laboratory supplies and outside services. Our manufacturing and development chemistry function is responsible for providing drug supplies to antisense drug development and our collaboration partners. Our manufacturing procedures include testing to satisfy good laboratory and good manufacturing practice requirements.

Our manufacturing and development chemistry expenses were as follows (in millions):

	Three Months Ended March 31,	
	2023	2022
Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	$ 14.7	$ 16.3
Non-cash compensation expense related to equity awards	2.1	2.7
Total manufacturing and development chemistry expenses	$ 16.8	$ 19.0

R&D Support

In our research, development and patent expenses, we include support costs such as rent, repair and maintenance for buildings and equipment, utilities, depreciation of laboratory equipment and facilities, amortization of our intellectual property, information technology costs, procurement costs and waste disposal costs. We call these costs R&D support expenses.

The following table sets forth information on R&D support expenses (in millions):

	Three Months Ended March 31,	
	2023	2022
Personnel costs	$ 6.5	$ 5.1
Occupancy	7.3	4.0
Patent expenses	1.1	0.7
Insurance	0.9	0.9
Computer software and licenses	0.6	0.6
Other	2.6	2.5
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	19.0	13.8
Non-cash compensation expense related to equity awards	3.8	3.4
Total R&D support expenses	$ 22.8	$ 17.2

R&D support expenses, excluding non-cash compensation expense related to equity awards, increased in the three months ended March 31, 2023 compared to the same period in 2022. The increase was primarily related to increased occupancy and personnel costs to support advancing our pipeline and our technology. In October 2022, we executed a sale and leaseback transaction for our headquarters in Carlsbad, California. As a result, beginning in the fourth quarter of 2022, our occupancy costs increased because we began incurring rent expense for these facilities.

Selling, General and Administrative Expenses

SG&A expenses include personnel and outside costs associated with the pre-commercialization and commercialization activities for our medicines and costs to support our company, our employees and our stockholders including, legal, human resources, investor relations, and finance. Additionally, we include in selling, general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation and utilities costs that we need to support the corporate functions listed above. We also include fees we owe under our in-licensing agreements related to SPINRAZA.

The following table sets forth information on SG&A expenses (in millions):

	Three Months Ended March 31,	
	2023	**2022**
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 38.2	$ 27.1
Non-cash compensation expense related to equity awards	7.3	7.0
Total selling, general and administrative expenses	$ 45.5	$ 34.1

SG&A expenses, excluding non-cash compensation expense related to equity awards, increased in the three months ended March 31, 2023 compared to the same period in 2022 due to increased expenses related to our go-to-market activities for eplontersen, olezarsen and donidalorsen.

Investment Income

Investment income for the three months ended March 31, 2023 was $18.6 million compared to $2.0 million for the same period in 2022. Our investment income increased primarily due to an increase in interest rates associated with our investments in debt securities and an increase in our cash balance during the three months ended March 31, 2023 compared to the same period in 2022. Our cash balance increased due to the $500 million upfront payment we received in January 2023 from our royalty purchase agreement with Royalty Pharma Investments, or Royalty Pharma.

Interest Expense

The following table sets forth information on interest expense (in millions):

	Three Months Ended March 31,	
	2023	**2022**
Convertible notes:		
Non-cash amortization of debt issuance costs	$ 1.3	$ 1.3
Interest expense payable in cash	0.2	0.2
Interest on mortgage for primary R&D and manufacturing facilities	0.1	0.6
Total interest expense	$ 1.6	$ 2.1

Interest Expense Related to Sale of Future Royalties

We recorded $15.5 million of interest expense related to the sale of future royalties in the three months ended March 31, 2023 as a result of the Royalty Pharma transaction, in which we sold a minority interest in our future royalties to Royalty Pharma for a $500 million upfront payment and $625 million of potential future payments. Refer to Part I, Item 1, Note 10, *Liability Related to Sale of Future Royalties*, in the Notes to our condensed consolidated financial statements for further details.

Loss on Investments

We recorded a net loss on investments of $0.5 million for the three months ended March 31, 2023 compared to $6.6 million for the same period in 2022 due to changes in the fair value of our investments in privately held and publicly traded biotechnology companies.

Income Tax Expense

Beginning in 2022, the Tax Cuts and Jobs Act of 2017, or TCJA, requires taxpayers to amortize research and development expenditures over five years pursuant to Internal Revenue Code, or IRC, Section 174. Additionally, we expect to reflect the royalty purchase agreement with Royalty Pharma as a taxable sale, requiring us to include the proceeds from the sale, net of currently deductible issuance costs, as taxable income in 2023.

We recorded income tax expense of $11.4 million and $1.1 million for the three months ended March 31, 2023 and 2022, respectively. The increase in income tax expense for the three months ended March 31, 2023, compared to the same period in 2022, relates primarily to the impact of the Royalty Pharma transaction.

Net Loss and Net Loss per Share

We had a net loss of $124.3 million for the three months ended March 31, 2023 compared to net loss of $65.2 million for the same period in 2022, which reflects the fluctuations discussed above. Our basic and diluted net loss per share for the three months ended March 31, 2023 and 2022 was $0.87 and $0.46, respectively.

Liquidity and Capital Resources

We have financed our operations primarily from research and development collaborative agreements. We also finance our operations from commercial revenue from SPINRAZA royalties and TEGSEDI and WAYLIVRA commercial revenue. From our inception through March 31, 2023, we have earned approximately $6.6 billion in revenue. We have also financed our operations through the sale of our equity securities, the issuance of long-term debt and the sale of future royalties. From the time we were founded through March 31, 2023, we have raised net proceeds of approximately $2.1 billion from the sale of our equity securities. Additionally, from our inception through March 31, 2023, we have borrowed approximately $2.1 billion under long-term debt arrangements and received proceeds of $0.5 billion from the sale of future royalties to finance a portion of our operations.

Our cash, cash equivalents and short-term investments, working capital and long-term obligations increased from December 31, 2022 to March 31, 2023. As discussed above, in the first quarter of 2023, we received an upfront payment of $500 million when we entered into a royalty purchase agreement with Royalty Pharma and recorded a corresponding long-term liability related to the sale of future royalties.

The following table summarizes our contractual obligations, excluding our liability related to the sale of future royalties, as of March 31, 2023. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

Contractual Obligations	**Payments Due by Period (in millions)**		
(selected balances described below)	**Total**	**Less than 1 year**	**More than 1 year**
0 % Notes (principal payable)	$ 632.5	$ —	$ 632.5
0.125% Notes (principal and interest payable)	550.2	0.7	549.5
Operating leases	294.6	20.1	274.5
Building mortgage payments (principal and interest payable)	10.6	0.5	10.1
Other obligations (principal and interest payable)	0.8	0.1	0.7
Total	$ 1,488.7	$ 21.4	$ 1,467.3

Our contractual obligations consist primarily of our convertible debt. In addition, we also have facility leases, a facility mortgage, equipment financing arrangements and other obligations. Due to the uncertainty with respect to the timing of future cash flows associated with our unrecognized tax benefits, we are unable to make reasonably reliable estimates of the period of cash settlement with the respective taxing authorities. Therefore, we have excluded our gross unrecognized tax benefits from our contractual obligations table above. We have not entered into, nor do we currently have, any off-balance sheet arrangements (as defined under SEC rules).

Convertible Debt and Call Spread

Refer to Part I, Item 1, Note 11, *Convertible Debt*, in the Notes to our condensed consolidated financial statements for the significant terms of each convertible debt instrument.

Operating Facilities

In July 2017, we purchased the building that houses our primary R&D facility for $79.4 million and our manufacturing facility for $14.0 million. We financed the purchase of these two facilities with mortgage debt of $60.4 million in total. Our primary R&D facility mortgage had an interest rate of 3.88 percent. Our manufacturing facility mortgage has an interest rate of 4.20 percent. During the first five years of both mortgages, we were only required to make interest payments. We began making principal payments in 2022. Our manufacturing facility mortgage matures in August 2027.

In October 2022, we concurrently entered into two purchase and sale agreements with a real estate investor. Under the agreements, we sold and leased back the facilities at our headquarters location in Carlsbad, California and will sell, subject to meeting certain closing conditions, two lots of undeveloped land adjacent to our headquarters. We sold the facilities at our headquarters, which includes our primary R&D facility, for a total purchase price of $263.4 million and we expect to receive total proceeds of $33.0 million upon the close of the sale of the two lots. We used a portion of the sale proceeds to extinguish our outstanding mortgage debt on our primary R&D facility of $51.3 million.

Operating Leases

Refer to our Leases accounting policy in Part IV, Item 15, Note 1 of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2022 for further details on our operating leases.

Liability Related to Sale of Future Royalties

Refer to Part I, Item 1, Note 10, *Liability Related to Sale of Future Royalties*, in the Notes to our condensed consolidated financial statements for further details on our royalty purchase agreement with Royalty Pharma.

Other Obligations

In addition to contractual obligations, we had outstanding purchase orders as of March 31, 2023 for the purchase of services, capital equipment and materials as part of our normal course of business.

We may enter into additional collaborations with partners which could provide for additional revenue to us and we may incur additional cash expenditures related to our obligations under any of the new agreements we may enter into. We currently intend to use our cash, cash equivalents and short-term investments to finance our activities. However, we may also pursue other financing alternatives, like issuing additional shares of our common stock, issuing debt instruments, refinancing our existing debt, or securing lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to changes in interest rates primarily from our investments in certain short-term investments. We primarily invest our excess cash in highly liquid short-term investments of the U.S. Treasury and reputable financial institutions, corporations, and U.S. government agencies with strong credit ratings. We typically hold our investments for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we are not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

We are also exposed to changes in foreign currency exchange rates as we have foreign subsidiaries with functional currencies other than the U.S. dollar. We translate our subsidiaries' functional currencies into our reporting currency, the U.S. dollar. As a result, our financial position, results of operations and cash flows can be affected by market fluctuations in the foreign currencies to U.S. dollar exchange rate, which are difficult to predict. A hypothetical 10 percent change in foreign exchange rates during any of the periods presented would not have had a material impact on our condensed consolidated financial statements.

ITEM 4. CONTROLS AND PROCEDURES

We maintain disclosure controls and procedures that are designed to ensure that information we are required to disclose in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. We design and evaluate our disclosure controls and procedures recognizing that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance and not absolute assurance of achieving the desired control objectives.

As of our most recently completed fiscal year and as of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of March 31, 2023. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2023.

We also performed an evaluation of any changes in our internal controls over financial reporting that occurred during our last fiscal quarter and that have materially affected, or are reasonably likely to materially affect, our internal controls over financial reporting. We conducted this evaluation under the supervision of and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. That evaluation did not identify any changes in our internal controls over financial reporting that occurred during our latest fiscal quarter and that have materially affected, or are reasonably likely to materially affect, our internal controls over financial reporting.

PART II — OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

For details of legal proceedings, refer to Part I, Item 1, Note 12, *Legal Proceedings*, in the Notes to our condensed consolidated financial statements.

ITEM 1A. RISK FACTORS

Investing in our securities involves a high degree of risk. You should carefully consider the following information about the risks described below, together with the other information contained in this report and in our other public filings in evaluating our business. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment. We have marked with an asterisk those risk factors that reflect substantive changes from the risk factors included in our Annual Report on Form 10-K for the year ended December 31, 2022.

Summary of Risk Factors

There are a number of risks related to our business and our securities. Some of the principal risks related to our business include the following:

- Our ability to generate substantial revenue from the sale of our medicines;
- The availability of adequate coverage and payment rates for our medicines;
- Our and our partners' ability to compete effectively;
- Our ability to successfully manufacture our medicines;
- Our ability to successfully develop and obtain marketing approvals for our medicines;
- Our ability to secure and maintain effective corporate partnerships;
- Our ability to sustain cash flows and achieve consistent profitability;
- Our ability to protect our intellectual property;
- Our ability to maintain the effectiveness of our personnel;
- The impacts of the COVID-19 pandemic and ongoing war between Russia and Ukraine; and
- The other factors set forth below.

Risks Related to the Commercialization of our Medicines

We have limited experience as a company in commercializing medicines and we will have to invest significant resources to develop our capabilities. If we are unable to establish effective marketing, sales, market access, distribution, and related functions, or enter into agreements with third parties to commercialize our medicines, we may not be able to generate revenue from our medicines.

We currently rely on third parties for the commercialization of our marketed medicines, have limited experience as a company in commercializing medicines and will have to invest significant financial and management resources to develop the infrastructure required to successfully commercialize our medicines. There are significant risks involved in building and managing a sales organization, including our ability to hire, retain and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel, and effectively manage a geographically dispersed sales and marketing team. We will also need to scale-up existing internal support functions to aid our commercialization efforts, in particular, regulatory affairs and medical affairs. Any failure to effectively build or maintain the infrastructure required to successfully commercialize our medicines, including our sales, marketing, market access, distribution, and related capabilities, or scale-up our existing support functions, could adversely impact the revenue we generate from our medicines. In addition, if we choose to rely on third parties to assist us in commercializing our medicines, we may not be able to enter into collaborations or hire consultants or external service providers on acceptable financial terms, or at all. If we continue to engage third parties to assist us in the commercialization of our medicines, our product revenues and profitability may be lower than if we commercialized such medicines ourselves.

If the market does not accept our medicines, including QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and our other medicines in development, we are not likely to generate substantial revenues or become consistently profitable.

Even if our medicines are authorized for marketing, our success will depend upon the medical community, patients and third-party payers accepting our medicines as medically useful, cost-effective, safe and convenient. Even when the FDA or foreign regulatory authorities authorize our or our partners' medicines for commercialization, doctors may not prescribe our medicines to treat patients. Furthermore, we and our partners may not successfully commercialize additional medicines.

Additionally, in many of the markets where we or our partners may sell our medicines in the future, if we or our partners cannot agree with the government or other third-party payers regarding the price we can charge for our medicines, we may not be able to sell our medicines in that market. Similarly, cost control initiatives by governments or third-party payers could decrease the price received for our medicines or increase patient coinsurance to a level that makes our medicines, including QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, and our medicines in development, economically unviable. If the pricing of any of our medicines decreases for any reason, it will reduce our revenue for such medicine. For example, Biogen has disclosed that SPINRAZA revenue has decreased in part due to lower pricing in the U.S. and certain rest of world markets.

The degree of market acceptance for our medicines, including QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, and our medicines in development, depends upon a number of factors, including the:

- receipt and scope of marketing authorizations;
- establishment and demonstration in the medical and patient community of the efficacy and safety of our medicines and their potential advantages over competing products;
- cost and effectiveness of our medicines compared to other available therapies;
- patient convenience of the dosing regimen for our medicines; and
- reimbursement policies of government and third-party payers.

Based on the profile of our medicines, physicians, patients, patient advocates, payers or the medical community in general may not accept or use any of the medicines that we may develop.

For example, TEGSEDI requires periodic blood and urine monitoring, is available in the U.S. only through a REMS program, and the product label in the U.S. has a boxed warning for thrombocytopenia and glomerulonephritis. Our main competitors in the U.S. market for TEGSEDI are patisiran and vutrisiran, both marketed by Alnylam Pharmaceuticals, Inc. Neither patisiran nor vutrisiran has a boxed warning nor does either require use of a REMS program. Additionally, the product label for WAYLIVRA in the European Union, or EU, requires regular blood monitoring. In each case, these label requirements have negatively affected our ability to attract and retain patients for these medicines. If we or our partner cannot effectively maintain patients on TEGSEDI or WAYLIVRA, including due to limitations or restrictions on the ability to conduct periodic blood and urine monitoring of our patients as a result of the COVID-19 pandemic, we may not be able to generate substantial revenue from TEGSEDI or WAYLIVRA sales.

If government or other third-party payers fail to provide adequate coverage and payment rates for our medicines, including QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, and our medicines in development, our revenue will be limited.*

In both domestic and foreign markets, sales of our current and future products will depend in part upon the availability of coverage and reimbursement from third-party payers. The majority of patients in the U.S. who would fit within our target patient populations for our medicines have their healthcare supported by a combination of Medicare coverage, other government health programs such as Medicaid, managed care providers, private health insurers and other organizations. Coverage decisions may depend upon clinical and economic standards that disfavor new medicines when more established or lower cost therapeutic alternatives are already available or subsequently become available. Assuming coverage is approved, the resulting reimbursement payment rates might not be enough to make our medicines affordable. Even if favorable coverage status and adequate reimbursement rates are attained, less favorable coverage policies and reimbursement rates may be implemented in the future. Accordingly, QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, and our medicines in development, will face competition from other therapies and medicines for limited financial resources. We or our partners may need to conduct post-marketing studies to demonstrate the cost-effectiveness of any future products to satisfy third-party payers. These studies might require us to commit a significant amount of management time and financial and other resources. In addition, third-party payers may never consider our future products as cost-effective and adequate third-party coverage and reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development.

Third-party payers, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the U.S., no uniform policy of coverage and reimbursement for medicines exists among third-party payers. Therefore, coverage and reimbursement for medicines can differ significantly from payer to payer. For example, the Affordable Care Act, or ACA, was passed in March 2010, and substantially changed the way healthcare is financed by both governmental and private insurers and continues to significantly impact the U.S. pharmaceutical industry. There have been judicial and Congressional challenges to certain aspects of the ACA, as well as efforts to repeal or replace certain aspects of the ACA. It is unclear how future litigation and healthcare reform measures will impact the ACA and our business.

Further, we believe that future coverage, reimbursement and pricing will likely be subject to increased restrictions both in the U.S. and in international markets. In the U.S., recent health reform measures have resulted in reductions in Medicare and other healthcare funding, and there have been several recent U.S. Congressional inquiries, legislation and executive orders designed to, among other things, reduce drug prices, increase competition, lower out-of-pocket drug costs for patients, and foster scientific innovation to promote better health care and improved health. In addition, the Inflation Reduction Act of 2022, or the IRA, among other things, allows the U.S. Department of Health and Human Services, or HHS, to negotiate the price of certain single-source drugs covered under Medicare and imposes rebates under Medicare Part B and Medicare Part D. In an effort to curb Medicare patients' out-of-pocket costs for prescription drugs, the Part D redesign legislation requires manufacturers to contribute to the catastrophic coverage phase for Part D drugs as discounts through a manufacturer discount program. Furthermore, any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payers. Our future product sales may be subject to additional discounts from list price in the form of rebates and discounts provided to 340B covered entities. Changes to the 340B program or to Medicare or Medicaid programs at the federal or state level, including outcomes of ongoing litigation in our industry, may impact our product prices and rebate liability. Further, in February 2023, in response to President Biden's executive order released in October 2022, the Secretary of the U.S. Department of HHS selected three new models for testing by the Centers for Medicare & Medicaid Services Innovation Center to help lower the high cost of drugs, promote accessibility to life-changing drug therapies and improve quality of care. It is unclear whether or how these selected models or similar policy initiatives will impact prescription drug pricing in the future.

At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Third-party coverage and reimbursement for medicines may not be available or adequate in either the U.S. or international markets, which would negatively affect the potential commercial success of our products, our revenue and our profits.

If we or our partners fail to compete effectively, our medicines, including QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA, and eplontersen, and our medicines in development, will not generate significant revenues.

Our competitors engage in drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. In addition, other companies are engaged in developing RNA-targeted technology. Our competitors may succeed in developing medicines that are:

- priced lower than our medicines;
- reimbursed more favorably by government and other third-party payers than our medicines;
- safer than our medicines;
- more effective than our medicines; or
- more convenient to use than our medicines.

These competitive developments could make our medicines, including QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, and our medicines in development, obsolete or non-competitive.

Certain of our partners are pursuing other technologies or developing other medicines either on their own or in collaboration with others, including our competitors, to treat some of the same diseases our own collaborative programs target. Competition may negatively impact a partner's focus on and commitment to our medicines and, as a result, could delay or otherwise negatively affect the commercialization of our medicines, including QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical studies of new pharmaceutical products, in obtaining FDA and other regulatory authorizations of such products and in commercializing such products. Accordingly, our competitors may succeed in obtaining regulatory authorization for products earlier than we do or more successfully commercialize their products.

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization in certain geographic markets of products against targets that are also targets of products in our development pipeline. For example:

- Onasemnogene abeparvovec and risdiplam compete with SPINRAZA;
- Patisiran, tafamidis, tafamidis meglumine and vutrisiran compete with TEGSEDI and could compete with eplontersen;
- Acoramidis could compete with TEGSEDI and eplontersen;
- ARO-APOC3, lomitapide and pegozafermin could compete with WAYLIVRA and olezarsen;
- Lanadelumab-flyo, C1 esterase inhibitor, berotralstat, C1 esterase inhibitor subcutaneous, garadacimab, and NTLA-2002 could compete with donidalorsen;
- Olpasiran and SLN360 could compete with pelacarsen; and
- NI-204 could compete with QALSODY.

SPINRAZA injection for intrathecal use is an antisense medicine indicated for the treatment of SMA patients of all ages approved in over 50 countries. Specifically, SPINRAZA faces competition from onasemnogene abeparvovec, a gene therapy product that was approved in the U.S. in May 2019 and in the EU in May 2020 for the treatment of SMA, as well as risdiplam, an oral product for the treatment of SMA that was approved in the U.S. in August 2020 and in the EU in March 2021. Biogen has disclosed that SPINRAZA revenue has decreased primarily due to a reduction in demand as a result of increased competition and that future sales of SPINRAZA may be adversely affected by competing products.

Additionally, companies that are developing medicines that target the same patient populations as our medicines in development may compete with us to enroll participants in the clinical trials for such medicines, which could make it more difficult for us to complete enrollment for these clinical trials.

Our medicines could be subject to regulatory limitations following approval.

Following approval of a medicine, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of medicines. Promotional communications regarding prescription medicines must be consistent with the information in the product's approved labeling. We or our partners may not obtain the labeling claims necessary or desirable to successfully commercialize our medicines, including QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, and our medicines in development.

The FDA and foreign regulatory bodies have the authority to impose significant restrictions on an approved medicine through the product label and on advertising, promotional and distribution activities. For example:

- in the U.S., TEGSEDI's label contains a boxed warning for thrombocytopenia and glomerulonephritis;
- TEGSEDI requires periodic blood and urine monitoring; and
- in the U.S., TEGSEDI is available only through a REMS program.

Prescription medicines may be promoted only for the approved indication(s) in accordance with the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

In addition, when approved, the FDA or a foreign regulatory authority may condition approval on the performance of post-approval clinical studies or patient monitoring, which could be time consuming and expensive. For example, in connection with the conditional marketing approval for WAYLIVRA in the EU, we are required to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. If the results of such post-marketing studies are not satisfactory, the FDA, EC or other foreign regulatory authorities may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and time consuming to fulfill.

If we or others identify side effects after any of our medicines are on the market, or if manufacturing problems occur subsequent to regulatory approval, or if we, our manufacturers or our partners fail to comply with regulatory requirements, we or our partners may, among other things, lose regulatory approval and be forced to withdraw products from the market, need to conduct additional clinical studies, incur restrictions on the marketing, distribution or manufacturing of the product, and/or change the labeling of our medicines.

We depend on our collaboration with Biogen for the development and commercialization of SPINRAZA.

We have entered into a collaborative arrangement with Biogen to develop and commercialize SPINRAZA. We entered into this collaboration primarily to:

- fund our development activities for SPINRAZA;
- seek and obtain regulatory approvals for SPINRAZA; and
- successfully commercialize SPINRAZA.

We are relying on Biogen to obtain additional regulatory approvals for SPINRAZA, generate additional clinical data for SPINRAZA, manufacture, and continue to successfully commercialize SPINRAZA. In general, we cannot control the amount and timing of resources that Biogen devotes to our collaboration. If Biogen fails to further develop SPINRAZA, obtain additional regulatory approvals for SPINRAZA, manufacture or continue to successfully commercialize SPINRAZA, or if Biogen's efforts in any of these respects are ineffective, revenues for SPINRAZA would be negatively affected.

In addition, our collaboration with Biogen may not continue for various reasons. Biogen can terminate our collaboration at any time. If Biogen stops developing or commercializing SPINRAZA, we would have to seek or spend additional funding, and SPINRAZA's commercialization may be harmed.

We depend on our collaboration with AstraZeneca for the joint development and commercialization of eplontersen.

We have entered into a collaborative arrangement with AstraZeneca to develop and commercialize eplontersen. Under the terms of the collaboration agreement, we and AstraZeneca will co-develop and co-commercialize eplontersen in the U.S. and AstraZeneca will have the sole right to commercialize eplontersen in all other countries, except for certain Latin American countries. Prior to co-commercializing eplontersen in the U.S., we will need to negotiate a co-commercialization agreement with AstraZeneca to govern the parties' performance of co-commercialization, which agreement will include a commercial plan and budget. As a company we do not have experience with co-commercialization arrangements. We also do not have control over the amount and timing of resources that AstraZeneca devotes to our collaboration, particularly outside of the U.S. If the co-commercialization arrangement for eplontersen is not successful for any reason, eplontersen may not meet our commercial objectives and our revenues for eplontersen may be limited.

In addition, a Joint Steering Committee, or JSC, having equal membership from us and AstraZeneca, and various subcommittees oversee and coordinate the development, manufacturing, commercialization and other exploitation activities for eplontersen in the U.S. by mutual agreement. If any subcommittee cannot reach unanimous agreement on any matter within its respective scope of authority, such matter may be referred to the JSC for resolution. If the JSC cannot come to a mutual agreement on any particular matter, this could delay our ability to develop or commercialize eplontersen.

If we are not successful in expanding our manufacturing capabilities or cannot manufacture our medicines or contract with a third party to manufacture our medicines at costs that allow us to charge competitive prices to buyers, we cannot market our products profitably.

To successfully commercialize any of our medicines, we need to optimize and manage large-scale commercial manufacturing capabilities either on a standalone basis or through a third-party manufacturer. As our drug development and commercial pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. To that end, we have begun work on a new manufacturing facility in Oceanside, California that will expand our manufacturing infrastructure. We will incur substantial expenditures to build our new manufacturing facility and, following its completion, will likely need to hire and train additional staff to operate the facility. If we are not successful in executing this expansion, it could limit our ability to meet our manufacturing requirements and commercial objectives in the future.

In addition, we have limited experience manufacturing pharmaceutical products of the chemical class represented by our medicines, called oligonucleotides, on a commercial scale for the systemic administration of a medicine. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our medicines, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our drug costs. We or our partners may not be able to manufacture our medicines at a cost or in quantities necessary to make commercially successful products.

Manufacturers, including us, must adhere to the FDA's cGMP regulations and similar regulations in foreign countries, which the applicable regulatory authorities enforce through facilities inspection programs. We, our partners and our contract manufacturers may not comply or maintain compliance with cGMP, or similar foreign regulations. Non-compliance could significantly delay or prevent receipt of marketing authorizations for our medicines, including authorizations for QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, and our medicines in development, or could result in enforcement action after authorization that might limit the commercial success of our medicines, including QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, and our medicines in development.

We rely on third-party manufacturers to supply the drug substance and drug product for TEGSEDI and drug product for WAYLIVRA. Any delays or disruption to our own or third-party commercial manufacturing capabilities, including any interruption to our supply chain as a result of the COVID-19 pandemic or the ongoing war between Russia and Ukraine, could limit the commercial success of our medicines.

We are relying on third parties to market, sell and distribute TEGSEDI and WAYLIVRA.

We have entered into agreements with third parties to commercialize TEGSEDI and WAYLIVRA as follows:

- In April 2021, we entered into a distribution agreement with Sobi to commercialize TEGSEDI in the U.S. and Canada;
- In December 2020, we entered into a distribution agreement with Sobi to commercialize TEGSEDI and WAYLIVRA in Europe; and
- In August 2018, we granted PTC the exclusive right to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries.

We are relying on Sobi and PTC to effectively market, sell and distribute TEGSEDI and WAYLIVRA and have less control over sales efforts and may receive less revenue than if we commercialized TEGSEDI or WAYLIVRA by ourselves. If Sobi or PTC does not successfully commercialize TEGSEDI or WAYLIVRA, including as a result of delays or disruption caused by the COVID-19 pandemic, we may receive limited revenue for TEGSEDI or WAYLIVRA in the U.S., Canada, Europe, Latin America or certain Caribbean countries, which could adversely affect our business, prospects, financial condition and results of operations.

Risks Related to the Development and Regulatory Approval of our Medicines

If we or our partners fail to obtain regulatory approval for our medicines and additional approvals for SPINRAZA, TEGSEDI and WAYLIVRA, we or our partners cannot sell them in the applicable markets.

We cannot guarantee that any of our medicines will be considered safe and effective or will be approved for commercialization. In addition, it is possible that SPINRAZA, TEGSEDI and WAYLIVRA may not be approved in additional markets or for additional indications. We and our partners must conduct time-consuming, extensive and costly clinical studies to demonstrate the safety and efficacy of each of our medicines before they can be approved or receive additional approvals for sale. We and our partners must conduct these studies in compliance with FDA regulations and with comparable regulations in other countries.

We and our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for our medicines. It is possible that regulatory agencies will not approve our medicines for marketing or SPINRAZA, TEGSEDI or WAYLIVRA in additional markets or for additional indications. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, or our medicines in development, the agency will not approve the specific medicine or will require additional studies, which could be time consuming and expensive and delay or harm commercialization of the medicine. For example, in August 2018 we received a complete response letter from the FDA regarding the new drug application for WAYLIVRA in which the FDA determined that the safety concerns identified with WAYLIVRA in our clinical development program outweighed the expected benefits of triglyceride lowering in patients with FCS. We also received a Non-W from Health Canada for WAYLIVRA in November 2018.

The FDA or other comparable foreign regulatory authorities can delay, limit or deny approval of a medicine for many reasons, including:

- such authorities may disagree with the design or implementation of our clinical studies;
- we or our partners may be unable to demonstrate to the satisfaction of the FDA or other regulatory authorities that a medicine is safe and effective for any indication;
- such authorities may not accept clinical data from studies conducted at clinical facilities that have deficient clinical practices or that are in countries where the standard of care is potentially different from the U.S.;
- we or our partners may be unable to demonstrate that our medicine's clinical and other benefits outweigh its safety risks to support approval;
- such authorities may disagree with the interpretation of data from preclinical or clinical studies;
- such authorities may find deficiencies in the manufacturing processes or facilities of third-party manufacturers who manufacture clinical and commercial supplies for our medicines, or may delay the inspection of such facilities due to restrictions related to the COVID-19 pandemic; and
- the approval policies or regulations of such authorities or their prior guidance to us or our partners during clinical development may significantly change in a manner rendering our clinical data insufficient for approval.

Failure to receive marketing authorization for our medicines, or failure to receive additional marketing authorizations for SPINRAZA, TEGSEDI or WAYLIVRA, or delays in these authorizations, could prevent or delay commercial introduction of the medicine, and, as a result, could negatively impact our ability to generate revenue from product sales.

If the results of clinical testing indicate that any of our medicines are not suitable for commercial use, we may need to abandon one or more of our drug development programs.

Drug discovery and drug development have inherent risks and the historical failure rate for drugs is high. Antisense medicines are a relatively new approach to therapeutics. If we cannot demonstrate that our medicines are safe and effective for human use in the intended indication(s), we may need to abandon one or more of our drug development programs.

Even if our medicines are successful in preclinical and human clinical studies, the medicines may not be successful in late-stage clinical studies.

Successful results in preclinical or initial human clinical studies, including the Phase 2 results for some of our medicines in development, may not predict the results of subsequent clinical studies. If any of our medicines in Phase 3 clinical studies, including the studies of QALSODY, bepirovirsen, donidalorsen, eplontersen, ION363, olezarsen and pelacarsen, do not show sufficient efficacy in patients with the targeted indication, or if such studies are discontinued for any other reason, it could negatively impact our development and commercialization goals for these medicines and our stock price could decline.

In the past, we have invested in clinical studies of medicines that have not met the primary clinical endpoints in their Phase 3 studies or have been discontinued for other reasons. For example, in October 2021, Biogen reported that QALSODY (tofersen) did not meet the primary clinical endpoint in the Phase 3 VALOR study; however, trends favoring QALSODY were seen across multiple secondary and exploratory measures of disease activity and clinical function. In addition, in March 2021, Roche decided to discontinue dosing in the Phase 3 GENERATION HD1 study of tominersen in patients with manifest Huntington's disease based on the results of a pre-planned review of data from the Phase 3 study conducted by an unblinded Independent Data Monitoring Committee. Similar results could occur in clinical studies for our other medicines, including the studies of QALSODY, bepirovirsen, donidalorsen, eplontersen, ION363, olezarsen and pelacarsen.

There are a number of factors that could cause a clinical study to fail or be delayed, including:

- the clinical study may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical study due to adverse side effects of a medicine on subjects or lack of efficacy in the trial;
- we or our partners may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies;
- enrollment in our clinical studies may be slower than we anticipate;
- we or our partners, including our independent clinical investigators, contract research organizations and other third-party service providers on which we rely, may not identify, recruit and train suitable clinical investigators at a sufficient number of study sites or timely enroll a sufficient number of study subjects in the clinical study;
- the institutional review board for a prospective site might withhold or delay its approval for the study;
- people who enroll in the clinical study may later drop out due to adverse events, a perception they are not benefiting from participating in the study, fatigue with the clinical study process or personal issues;
- a clinical study site may deviate from the protocol for the study;
- the cost of our clinical studies may be greater than we anticipate;
- our partners may decide not to exercise any existing options to license and conduct additional clinical studies for our medicines; and
- the supply or quality of our medicines or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

The COVID-19 pandemic could make some of these factors more likely to occur.

In addition, our current medicines, including QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen are chemically similar to each other. As a result, a safety observation we encounter with one of our medicines could have, or be perceived by a regulatory authority to have, an impact on a different medicine we are developing. This could cause the FDA or other regulators to ask questions or take actions that could harm or delay our ability to develop and commercialize our medicines or increase our costs. For example, the FDA or other regulatory agencies could request, among other things, additional information or commitments before we can start or continue a clinical study, protocol amendments, increased safety monitoring, additional product labeling information, and post-approval commitments. This happened in connection with the conditional marketing approval for WAYLIVRA in the EU, as the EC is requiring us to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. We have ongoing post-marketing studies for WAYLIVRA and TEGSEDI and an EAP for WAYLIVRA. Adverse events or results from these studies or the EAPs could negatively impact our pending or future marketing approval applications for WAYLIVRA and TEGSEDI in patients with FCS or ATTRv-PN, respectively, or the commercial opportunity for WAYLIVRA or TEGSEDI.

Any failure or delay in our clinical studies, including the studies of QALSODY, bepirovirsen, donidalorsen, eplontersen, ION363, olezarsen and pelacarsen, could reduce the commercial potential or viability of our medicines.

We depend on third parties to conduct clinical studies for our medicines and any failure of those parties to fulfill their obligations could adversely affect our development and commercialization plans.

We depend on independent clinical investigators, contract research organizations and other third-party service providers to conduct our clinical studies for our medicines and expect to continue to do so in the future. For example, we use clinical research organizations, such as Icon Clinical Research Limited, Medpace, Inc., Parexel International Corporation, Syneos Health, Inc. and Thermo Fisher Scientific Inc. for the clinical studies for our medicines, including QALSODY, donidalorsen, eplontersen, ION363, olezarsen and pelacarsen. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees, but we are responsible for ensuring that such investigators conduct each of our clinical studies in accordance with the general investigational plan and approved protocols for the study. Third parties may not complete activities on schedule or may not conduct our clinical studies in accordance with regulatory requirements or our stated protocols. For example, some of our key vendors are experiencing labor shortages, which could impact their ability to perform services for us for certain of our clinical trials. The failure of these third parties to carry out their obligations, including as a result of delays or disruptions caused by the COVID-19 pandemic, or a termination of our relationship with such third parties, could delay or prevent the development, marketing authorization and commercialization of our medicines or additional marketing authorizations for TEGSEDI and WAYLIVRA.

In addition, while we do not have any clinical trial sites in Ukraine, we do have a limited number of clinical trial sites in Russia and surrounding countries that may be impacted by the ongoing war between Russia and Ukraine and could result in difficulties enrolling or completing our clinical trials in such areas on schedule. Furthermore, the U.S. and its European allies have imposed significant sanctions against Russia, including regional embargoes, full blocking sanctions, and other restrictions targeting major Russian financial institutions. The U.S. government has also indicated it will consider imposing additional sanctions and other similar measures in the future. Our ability to conduct clinical trials in Russia may become restricted under applicable sanctions laws, which would require us to identify alternative trial sites, and could increase our costs and delay the clinical development of certain of our medicines.

Since corporate partnering is a significant part of our strategy to fund the advancement and commercialization of our development programs, if any of our collaborative partners fail to fund our collaborative programs, or if we cannot obtain additional partners, we may have to delay or stop progress on our drug development programs.

To date, corporate partnering has played a significant role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize some of our unpartnered medicines. However, we may not be able to negotiate favorable collaborative arrangements for these drug programs. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our medicines could suffer.

Our corporate partners are developing and funding many of the medicines in our development pipeline. For example, we are relying on:

- AstraZeneca for the joint development and funding of eplontersen;
- Novartis for development and funding of pelacarsen;
- Biogen for development and funding of QALSODY;
- Biogen for additional studies of SPINRAZA; and
- GSK for development and funding of bepirovirsen.

If any of these pharmaceutical companies stops developing and funding these medicines, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these medicines on our own. Our collaborators can terminate their relationships with us under certain circumstances, many of which are outside of our control. For example, in 2022, Pfizer and Bayer decided to discontinue the clinical development programs for vupanorsen and fesomersen, respectively.

Even with funding from corporate partners, if our partners do not effectively perform their obligations under our agreements with them, it would delay or stop the progress of our drug development and commercial programs.

In addition to receiving funding, we enter into collaborative arrangements with third parties to:

- conduct clinical studies;
- seek and obtain marketing authorizations; and
- manufacture and commercialize our medicines.

Once we have secured a collaborative arrangement to further develop and commercialize one of our drug development programs, such as our collaborations with AstraZeneca, Biogen, GSK, Novartis, and Roche, these collaborations may not continue or result in commercialized medicines, or may not progress as quickly as we anticipated.

For example, a collaborator such as AstraZeneca, Biogen, GSK, Novartis, or Roche, could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products that may be competitive with the medicine that is part of the collaboration with us;
- pursue higher-priority programs or change the focus of its own development programs; or
- choose to devote fewer resources to our medicines than it does to its own medicines.

If any of these occur, it could affect our partner’s commitment to the collaboration with us and could delay or otherwise negatively affect the commercialization of our medicines, including QALSODY, SPINRAZA, bepirovirsen, eplontersen and pelacarsen.

We may not be able to benefit from orphan drug designation for our medicines.

In the U.S., under the Orphan Drug Act, the FDA may designate a medicine as an orphan drug if it is intended to treat a rare disease or condition affecting fewer than 200,000 individuals in the U.S. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process, but it can provide financial incentives, such as tax advantages and user-fee waivers, as well as longer regulatory exclusivity periods. The FDA has granted orphan drug designation to eplontersen for the treatment of patients with transthyretin-mediated amyloidosis and to ION582 for the treatment of patients with Angelman syndrome. The FDA and EMA have granted orphan drug designation to TEGSEDI for the treatment of patients with ATTRv-PN, to WAYLIVRA for the treatment of patients with FCS, and to tominersen for the treatment of patients with HD. In addition, the EMA has granted orphan drug designation to WAYLIVRA for the treatment of patients with FPL. Even if approval is obtained on a medicine that has been designated as an orphan drug, we may lose orphan drug exclusivity if the FDA or EMA determines that the request for designation was materially defective or if we cannot assure sufficient quantity of the applicable medicine to meet the needs of patients with the rare disease or condition, or if a competitor is able to gain approval for the same medicine in a safer or more effective form or that makes a major contribution to patient care. If we lose orphan drug exclusivity on any of our medicines, we may face increased competition and lose market share for such medicine.

Risks Associated with our Businesses as a Whole

Risks related to our financial condition

If we fail to obtain timely funding, we may need to curtail or abandon some of our programs.

Many of our medicines are undergoing clinical studies or are in the early stages of research and development. Most of our programs will require significant additional research, development, manufacturing, preclinical and clinical testing, marketing authorizations, preclinical activities and commitment of significant additional resources prior to their successful commercialization. In addition, as we commercialize more medicines on our own, we will need to invest significant financial resources to continue developing the infrastructure required to successfully commercialize our medicines, including the build-out of a new manufacturing facility. All of these activities will require significant cash. As of March 31, 2023, we had cash, cash equivalents and short-term investments equal to $2.3 billion. If we or our partners do not meet our goals to successfully commercialize our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, or to license certain medicines and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors such as:

- successful commercialization of SPINRAZA, TEGSEDI and WAYLIVRA;
- the profile and launch timing of our medicines, including QALSODY, bepirovirsen, donidalorsen, eplontersen, ION363, olezarsen and pelacarsen;
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements;
- continued scientific progress in our research, drug discovery and development programs;
- the size of our programs and progress with preclinical and clinical studies;
- the time and costs involved in obtaining marketing authorizations;
- competing technological and market developments, including the introduction by others of new therapies that address our markets; and
- our manufacturing requirements and capacity to fulfill such requirements.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available on acceptable terms or at all. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and the price, as well as the price of our other securities, may decline. If adequate funds are not available or not available on acceptable terms, we may have to cut back on one or more of our research, drug discovery or development programs. Alternatively, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies or medicines.

We have incurred losses, and our business will suffer if we fail to consistently achieve profitability in the future.

Because drug discovery and development require substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of March 31, 2023, we had an accumulated deficit of approximately $1.6 billion and stockholders' equity of approximately $0.5 billion. Most of our historical losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. Most of our income has historically come from collaborative arrangements, including commercial revenue from royalties and R&D revenue, with additional income from research grants and the sale or licensing of our patents, as well as interest income. We will now and continuing into the foreseeable future need to invest significant financial resources to develop capabilities to commercialize medicines on our own and expect that our income in the future will be driven primarily by commercial sales. If we do not earn substantial revenue from commercial sales, we may incur additional operating losses in the future, which could restrict our ability to successfully develop additional medicines or sustain future profitability.

We may not be entitled to obtain additional milestone payments under our royalty monetization agreement with Royalty Pharma.

In January 2023, we entered into a Royalty Purchase Agreement with Royalty Pharma Investments. In addition to the $500 million we received at closing, this agreement makes available to us up to an additional $625 million in milestone payments. However, these additional milestone payments are subject to satisfaction of certain conditions related to the regulatory approval or commercial sales of pelacarsen, in certain cases by specific deadlines. Should we not satisfy such conditions by the applicable deadlines, or if we fail to meet our obligations or default under this agreement, the actual amount of additional payments to us could be substantially less than the maximum amounts available thereunder.

Risks related to our intellectual property

If we cannot protect our patent rights or our other proprietary rights, others may compete more effectively against us.

Our success depends to a significant degree upon whether we can continue to develop, secure and maintain intellectual property rights to proprietary products and services. However, we may not receive issued patents on any of our pending patent applications in the U.S. or in other countries and we may not be able to obtain, maintain or enforce our patents and other intellectual property rights, any of which could impact our ability to compete effectively. In addition, the scope of any of our issued patents may not be sufficiently broad to provide us with a competitive advantage. Furthermore, other parties may successfully challenge, invalidate or circumvent our issued patents or patents licensed to us so that our patent rights do not create an effective competitive barrier or revenue source.

We cannot be certain that the U.S. Patent and Trademark Office, or U.S. PTO, and courts in the U.S. or the patent offices and courts in foreign countries will consider the claims in our patents and applications covering QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, or any of our medicines in development as patentable. Method-of-use patents protect the use of a product for the specified method. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products off-label. Although off-label prescriptions may infringe or contribute to the infringement of method-of-use patents, the practice is common and such infringement is difficult to prevent, even through legal action.

If we or any licensor partner loses or cannot obtain patent protection for QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA or eplontersen, or any of our medicines in development, it could have a material adverse impact on our business.

Intellectual property litigation could be expensive and prevent us from pursuing our programs.

From time to time, we have to defend our intellectual property rights. If we are involved in an intellectual property dispute, we may need to litigate to defend our rights or assert them against others. Disputes can involve arbitration, litigation or proceedings declared by the U.S. PTO or the International Trade Commission or foreign patent authorities. Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

If a third party claims that our medicines or technology infringe its patents or other intellectual property rights, we may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to needed intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or patent applications held by others that relate to our business. This is especially true since patent applications in the U.S. are filed confidentially for the first 18 months. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain.

Risks related to product liability

We are exposed to potential product liability claims, and insurance against these claims may not be available to us at a reasonable rate in the future or at all.

Our business exposes us to potential product liability risks that are inherent in the testing, manufacturing, marketing and sale of therapeutic products, including potential product liability claims related to SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development. We have clinical study insurance coverage and commercial product liability insurance coverage. However, this insurance coverage may not be adequate to cover claims against us, or be available to us at an acceptable cost, if at all. Regardless of their merit or eventual outcome, product liability claims may result in decreased demand for our medicines, injury to our reputation, withdrawal of clinical study volunteers and loss of revenues. Thus, whether or not we are insured, a product liability claim or product recall may result in losses that could be material.

Risks related to our personnel

The loss of key personnel, or the inability to attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.

We are dependent on the principal members of our management and scientific staff, and as we move towards commercializing medicines on our own, we will become increasingly dependent on the principal members of our commercial team. We do not have employment agreements with any of our employees that would prevent them from leaving us. The loss of our management, key scientific or commercial employees might slow the achievement of important research and development or commercial goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. In addition, failure to succeed in clinical studies may make it more challenging to recruit and retain qualified scientific personnel.

Risks related to the COVID-19 pandemic and other events

Our business may be adversely affected by pandemics, climate change, extreme weather events, earthquakes, war, civil or political unrest, terrorism or other catastrophic events.

Our business could be adversely affected by health epidemics in regions where we or our partners are commercializing our medicines, have concentrations of clinical trial sites or other business operations, and could cause disruption in the operations of third-party manufacturers and contract research organizations upon whom we rely. For example, some physician and hospital policies that were put in place as a result of the COVID-19 pandemic restricted in-person access by third parties, which in some cases impacted our commercialization efforts for TEGSEDI and WAYLIVRA. In addition, in December 2021, Novartis announced that enrollment for the Phase 3 HORIZON study had been delayed due to the COVID-19 pandemic. The COVID-19 pandemic continues to evolve, and while we believe we have not experienced material adverse effects to our business as a result of the COVID-19 pandemic, the ultimate impact of the COVID-19 pandemic or a similar health epidemic is highly uncertain.

In recent years, extreme weather events and changing weather patterns have become more common. As a result, we are potentially exposed to varying natural disaster or extreme weather risks such as hurricanes, tornadoes, fires, droughts, floods, or other events that may result from the impact of climate change on the environment. The potential impacts of climate change may also include increased operating costs associated with additional regulatory requirements and investments in reducing energy, water use and greenhouse gas emissions. In addition, we currently manufacture most of our research and clinical supplies in a manufacturing facility located in Carlsbad, California and will move such manufacturing to our new facility in Oceanside, California once it is built. We manufacture the finished drug product for TEGSEDI and WAYLIVRA at third-party contract manufacturers. Biogen manufactures the finished drug product for SPINRAZA. The facilities and the equipment we, our partners and our contract manufacturers use to research, develop and manufacture our medicines would be costly to replace and could require substantial lead time to repair or replace. Our facilities or those of our partners or contract manufacturers may be harmed by natural disasters or other events outside our control, such as earthquakes, war, civil or political unrest, deliberate acts of sabotage, terrorism or industrial accidents such as fire and explosion, whether due to human or equipment error, and if such facilities are affected by a disaster or other event, our development and commercialization efforts would be delayed. Although we possess property damage and business interruption insurance coverage, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all. In addition, our development and commercialization activities could be harmed or delayed by a shutdown of the U.S. government, including the FDA.

Risks related to cybersecurity

We are dependent on information technology systems, infrastructure and data, which exposes us to data security risks.

We are dependent upon our own and third-party information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems may make them vulnerable to service interruption or destruction, disruption of data integrity, malicious intrusion, or random attacks. Likewise, data privacy or security incidents or breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyber-attacks are increasing in their frequency, sophistication and intensity, with third-party phishing and social engineering attacks in particular increasing during the COVID-19 pandemic. In addition, the number and frequency of cybersecurity events globally may be heightened during times of geopolitical tension or instability between countries, including, for example, the ongoing war between Russia and Ukraine, as a result of which several companies (not including us) have reported recent cybersecurity events.

Cyber-attacks could include the deployment of harmful malware, denial-of-service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business partners face similar risks and any security breach of their systems could adversely affect our security posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and state breach notification laws and foreign law equivalents, subject us to financial penalties and mandatory and costly corrective action, require us to verify the correctness of database contents and otherwise subject us to litigation or other liability under laws and regulations that protect personal data, any of which could disrupt our business and result in increased costs or loss of revenue. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, our efforts may not prevent service interruptions or identify breaches in our systems that could adversely affect our business and operations and result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us.

Risks related to our securities and the global credit markets

If we do not progress in our programs as anticipated, the price of our securities could decrease.*

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain medicine will enter clinical trials, when we anticipate completing a clinical study, or when we anticipate filing an application for, or obtaining, marketing authorization, or when we or our partners plan to commercially launch a medicine. We base our estimates on present facts and a variety of assumptions, many of which are outside of our control, including the impacts of the COVID-19 pandemic. If we do not achieve milestones in accordance with our or our investors' or securities analysts' expectations, including milestones related to QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA, bepirovirsen, donidalorsen, eplontersen, ION363, olezarsen and pelacarsen, the price of our securities could decrease.

If the price of our securities continues to be highly volatile, this could make it harder to liquidate your investment and could increase your risk of suffering a loss.

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding March 31, 2023, the market price of our common stock ranged from $48.82 to $31.46 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical study results, technological innovations or new products being developed by us or our competitors, the commercial success of our approved medicines, governmental regulation, marketing authorizations, changes in payers' reimbursement policies, developments in patent or other proprietary rights and public concern regarding the safety of our medicines.

Broad market factors may materially harm the market price of our common stock irrespective of our operating performance. For example, the COVID-19 pandemic, the ongoing war between Russia and Ukraine and measures taken in response thereto and the recent failure of Silicon Valley Bank caused significant disruptions of global financial markets and resulted in increased volatility in the trading price of our common stock. In addition, industry factors may materially harm the market price of our common stock. Nasdaq, and the market for biotechnology companies in particular, have historically experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of the particular companies affected. The trading prices and valuations of these stocks, and of ours, may not be predictable. A loss of investor confidence in the market for biotechnology or pharmaceutical stocks or the stocks of other companies that investors perceive to be similar to us, the opportunities in the biotechnology and pharmaceutical market or the stock market in general, could depress our stock price regardless of our business, prospects, financial conditions or results of operations.

Provisions in our certificate of incorporation, convertible notes documents, call spread hedge transaction documents and Delaware law may prevent stockholders from receiving a premium for their shares.

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66 2/3 percent of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15 percent or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We have in the past, and may in the future, implement a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. In addition, our board of directors has the authority to fix the rights and preferences of, and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

The provisions of our convertible senior notes could make it more difficult or more expensive for a third party to acquire us. Upon the occurrence of certain transactions constituting a fundamental change, holders of the notes will have the right, at their option, to require us to repurchase all of their notes or a portion of their notes, which may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over the then-current market prices.

In April 2021, we completed a $632.5 million offering of 0% Notes and used a portion of the net proceeds from the issuance of the 0% Notes to repurchase $247.9 million of our 1% Notes for $257.0 million. In December 2019, we entered into privately negotiated exchange and/or subscription agreements with certain new investors and certain holders of our existing 1% Notes to exchange $375.6 million of our 1% Notes for $439.3 million of our 0.125% Notes, and to issue $109.5 million of our 0.125% Notes. Additionally, in connection with the pricing of our 0% Notes and 0.125% Notes, we entered into call spread transactions in which we purchased note hedges and sold warrants. Terminating or unwinding the call spread transactions could require us to make substantial payments to the counterparties under those agreements or may increase our stock price. The costs or any increase in stock price that may arise from terminating or unwinding such agreements could make an acquisition of our company significantly more expensive to the purchaser.

These provisions, as well as Delaware law, including Section 203 of the Delaware General Corporation Law, and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then-current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests.

Future sales of our common stock in the public market could adversely affect the trading price of our securities.

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. For example, we may issue approximately 17.5 million shares of our common stock upon conversion of our 0% Notes and 0.125% Notes, up to 10.9 million shares in connection with the warrant transactions we entered into in connection with the issuance of our 0% Notes, and up to 6.6 million shares in connection with the warrant transactions we entered into in connection with the issuance of our 0.125% Notes, in each case subject to customary anti-dilution adjustments. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

In addition, pursuant to the call spread transactions we entered into in connection with the pricing of our 0% Notes and 0.125% Notes, the counterparties are likely to modify their hedge positions from time to time at or prior to the conversion or maturity of the notes by purchasing and selling shares of our common stock, other of our securities, or other instruments, including over-the-counter derivative instruments, that they may wish to use in connection with such hedging, which may have a negative effect on the conversion value of those notes and an adverse impact on the trading price of our common stock. The call spread transactions are expected generally to reduce potential dilution to holders of our common stock upon any conversion of our 0% Notes or 0.125% Notes or offset any cash payments we are required to make in excess of the principal amount of the converted 0% Notes or 0.125% Notes, as the case may be. However, the warrant transactions could separately have a dilutive effect to the extent that the market value per share of our common stock exceeds the applicable strike price of the warrants.

Negative conditions in the global credit markets and financial services and other industries may adversely affect our business, financial condition or stock price.*

The global credit and financial markets have experienced extreme volatility and disruptions recently, including as a result of the ongoing COVID-19 pandemic and war between Russia and Ukraine and measures taken in response thereto, and more recently, the failure of Silicon Valley Bank. These disruptions can result in severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. If the current equity and credit markets deteriorate, it may make any necessary debt or equity financing more difficult, more costly and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our operations, growth plans, financial performance or stock price. In addition, our insurance carriers and insurance policies covering all aspects of our business may become financially unstable or may not be sufficient to cover any or all of our losses and may not continue to be available to us on acceptable terms, or at all. Furthermore, due to the rapidly rising inflation rate, we may experience significantly increased costs of goods and services for our business.

A variety of risks associated with operating our business and marketing our medicines internationally could adversely affect our business. In addition to our U.S. operations, we are commercializing TEGSEDI in the EU, Canada, Latin America and certain Caribbean countries, and WAYLIVRA in the EU, Latin America and certain Caribbean countries. We face risks associated with our international operations, including possible unfavorable regulatory, pricing and reimbursement, political, tax and labor conditions, which could harm our business. Because we have international operations, we are subject to numerous risks associated with international business activities, including:

- compliance with differing or unexpected regulatory requirements for our medicines and foreign employees;
- complexities associated with managing multiple payer reimbursement regimes, government payers or patient self-pay systems;
- difficulties in staffing and managing foreign operations;
- in certain circumstances, increased dependence on the commercialization efforts and regulatory compliance of third-party distributors or strategic partners;
- foreign government taxes, regulations and permit requirements;
- U.S. and foreign government tariffs, trade restrictions, price and exchange controls and other regulatory requirements;
- anti-corruption laws, including the Foreign Corrupt Practices Act, or the FCPA, and its equivalent in foreign jurisdictions;
- economic weakness, including inflation, natural disasters, war, events of terrorism, political instability or public health issues or pandemics, such as the COVID-19 pandemic, in particular foreign countries or globally;
- fluctuations in currency exchange rates, which could result in increased operating expenses and reduced revenue, and other obligations related to doing business in another country;
- compliance with tax, employment, privacy, immigration and labor laws, regulations and restrictions for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is more common than in the U.S.; and
- changes in diplomatic and trade relationships.

Our business activities outside of the U.S. are subject to the FCPA and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate, including the United Kingdom's Bribery Act 2010. In many other countries, the healthcare providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, any dealings with these prescribers and purchasers may be subject to regulation under the FCPA. There is no certainty that all employees and third-party business partners (including our distributors, wholesalers, agents, contractors and other partners) will comply with anti-bribery laws. In particular, we do not control the actions of manufacturers and other third-party agents, although we may be liable for their actions. Violation of these laws may result in civil or criminal sanctions, which could include monetary fines, criminal penalties, and disgorgement of past profits, which could have an adverse impact on our business and financial condition.

Risks related to compliance with laws

Our operations are subject to additional healthcare laws.

Our operations are subject to additional healthcare laws, including federal and state anti-kickback laws, false claims laws, transparency laws, such as the federal Sunshine Act, and health information privacy and security laws, which are subject to change at any time. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. Penalties for violations of applicable healthcare laws and regulations may include significant civil, criminal and administrative penalties, damages, disgorgement, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and additional reporting requirements and oversight if we enter into a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws. In addition, violations may also result in reputational harm, diminished profits and future earnings.

Because we use biological materials, hazardous materials, chemicals and radioactive compounds, if we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.

Our research, development and manufacturing activities involve the use of potentially harmful biological materials as well as materials, chemicals and various radioactive compounds that could be hazardous to human health and safety or the environment. We store most of these materials and various wastes resulting from their use at our facilities in Carlsbad, California pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause:

- interruption of our research, development and manufacturing efforts;
- injury to our employees and others;
- environmental damage resulting in costly clean up; and
- liabilities under federal, state and local laws and regulations governing health and human safety, as well as the use, storage, handling and disposal of these materials and resultant waste products.

In such an event, we may be held liable for any resulting damages, and any liability could exceed our resources. Although we carry insurance for pollution liability in amounts and types that we consider commercially reasonable, the coverage or coverage limits of our insurance policies may not be adequate. If our losses exceed our insurance coverage, our financial condition would be adversely affected.

Our business is subject to changing regulations for corporate governance and public disclosure that has increased both our costs and the risk of noncompliance.

Each year we are required to evaluate our internal control systems to allow management to report on and our Independent Registered Public Accounting Firm to attest to, our internal controls as required by Section 404 of the Sarbanes-Oxley Act. As a result, we continue to incur additional expenses and divert our management's time to comply with these regulations. In addition, if we cannot continue to comply with the requirements of Section 404 in a timely manner, we might be subject to sanctions or investigation by regulatory authorities, such as the SEC, the Public Company Accounting Oversight Board, or PCAOB, or The Nasdaq Global Select Market. Any such action could adversely affect our financial results and the market price of our common stock.

The SEC and other regulators have continued to adopt new rules and regulations and make additional changes to existing regulations that require our compliance. In July 2010, the Dodd-Frank Wall Street Reform and Protection Act, or the Dodd-Frank Act, was enacted, and in August 2022, the SEC adopted additional rules and regulations under the Dodd-Frank Act related to "say on pay" and proxy access. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which has and may in the future lead to additional compliance costs and impact the manner in which we operate our business.

Risks related to taxes

Our ability to use our net operating loss carryovers and certain other tax attributes may be limited.

Under the Internal Revenue Code of 1986, as amended, or the Code, a corporation is generally allowed a deduction for net operating losses, or NOLs, carried over from a prior taxable year. Under the Code, we can carry forward our NOLs to offset our future taxable income, if any, until such NOLs are used or expire. The same is true of other unused tax attributes, such as tax credits.

Under the current U.S. federal income tax law, U.S. federal NOLs generated in taxable years beginning after December 31, 2017 may be carried forward indefinitely, but the deductibility of such U.S. federal NOLs is limited to 80 percent of taxable income. It is uncertain if and to what extent various states will conform to current U.S. federal income tax law, and there may be periods during which states suspend or otherwise limit the use of NOLs for state income tax purposes.

In addition, under Sections 382 and 383 of the Code, and corresponding provisions of state law, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50 percentage-point cumulative change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change NOL carryforwards and other pre-change tax attributes to offset its post-change income or taxes may be limited. We may experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If an ownership change occurs and our ability to use our NOL carryforwards or other tax attributes is materially limited, it would harm our future operating results by effectively increasing our future tax obligations. As a result of the Akcea Merger, we are subject to the separate return limitation year, or SRLY, rules. Under the SRLY rules, our utilization of Akcea's pre-merger NOL and tax credit carryforwards is limited to the amount of income that Akcea contributes to our consolidated taxable income. The Akcea pre-merger tax attributes cannot be used to offset any of the income that Ionis contributes to our consolidated taxable income. In addition, at the state level, there may be periods during which the use of net operating losses is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

Our future taxable income could be impacted by changes in tax laws, regulations and treaties.

A change in tax laws, treaties or regulations, or their interpretation, of any country in which we operate could materially affect us.

We could be subject to additional tax liabilities.

We are subject to U.S. federal, state, local and foreign income taxes, sales taxes in the U.S., withholding taxes and transaction taxes in foreign jurisdictions. Significant judgment is required in evaluating our tax positions and our worldwide provision for taxes. During the ordinary course of business, there are many activities and transactions for which the ultimate tax determination is uncertain. In addition, our tax obligations and effective tax rates could be adversely affected by changes in the relevant tax, accounting and other laws, regulations, principles and interpretations, including those relating to income tax nexus, by recognizing tax losses or lower than anticipated earnings in jurisdictions where we have lower statutory rates and higher than anticipated earnings in jurisdictions where we have higher statutory rates, by changes in foreign currency exchange rates, or by changes in the valuation of our deferred tax assets and liabilities. We may be audited in various jurisdictions, and such jurisdictions may assess additional taxes, sales taxes and value-added taxes against us. Although we believe our tax estimates are reasonable, the final determination of any tax audits or litigation could be materially different from our historical tax provisions and accruals, which could have a material adverse effect on our operating results or cash flows in the period for which a determination is made.

ITEM 2. UNREGISTERED SALES OF EQUITY SECURITIES AND USE OF PROCEEDS

Not applicable.

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

ITEM 5. OTHER INFORMATION

Not applicable.

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Second Amended Non-Employee Director Compensation Policy.
10.2	Ionis Pharmaceuticals, Inc. Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, as amended on March 14, 2023.
10.3	Forms of Restricted Stock Unit Grant Notice and Restricted Stock Unit Agreement for Restricted Stock Units granted under the Ionis Pharmaceuticals, Inc. Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, as amended on March 14, 2023.
10.4	HTT Research, Development, Option and License Agreement among the Registrant, F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., dated as of April. 8, 2013.
10.5	Royalty Purchase Agreement by and between the Registrant, Akcea Therapeutics, Inc. and Royalty Pharma Investments 2019 ICAV dated as of January 9, 2023. Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
31.1	Certification by Chief Executive Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
31.2	Certification by Chief Financial Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
32.1*	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial statements from the Ionis Pharmaceuticals, Inc. Quarterly Report on Form 10-Q for the quarter ended March 31, 2023, formatted in Inline Extensible Business Reporting Language (iXBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of comprehensive income (loss), (iv) condensed consolidated statements of stockholders' equity, (v) condensed consolidated statements of cash flows and (vi) notes to condensed consolidated financial statements (detail tagged).
104	Cover Page Interactive Data File (formatted in iXBRL and included in exhibit 101).

* This certification is deemed not filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liability of that section, nor shall it be deemed incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signatures	Title	Date
/s/ BRETT P. MONIA Brett P. Monia, Ph.D.	Director and Chief Executive Officer (Principal executive officer)	May 3, 2023
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	May 3, 2023

Exhibit 10.1

Second Amended Non-Employee Director Compensation Policy
As of April 24, 2023

Ionis Pharmaceuticals, Inc. ("***Ionis***") values the contributions made by its Board of Directors. In recognition of these valuable contributions, Ionis will provide each non-employee Director with the compensation described in this policy.

Cash Compensation

Each non-employee Director will receive cash compensation based on his or her role on the Board and Board committees as follows:

Role	Cash Compensation
Board Member (base retainer)	$ 60,000(1)
Non-Executive Chairman of the Board (additional)	$ 40,000
Independent Lead Director (additional)	$ 40,000
Committee Chair (additional):	
-Audit	$ 24,000
-Compliance	$ 20,000
-Compensation	$ 20,000
-Finance	$ 20,000
-Nominating, Governance and Review	$ 20,000
-Science/Medical	$ 20,000
Committee Member (additional):	
-Audit	$ 12,000
-Compliance	$ 10,000
-Compensation	$ 10,000
-Finance	$ 10,000
-Nominating, Governance and Review	$ 10,000
-Science/Medical	$ 10,000

(1) Before March 31, 2024 this annual base cash retainer for each non-employee Director (not including fees for Non-Executive Chair, Independent Lead Director, Committee Chair or Committee Member) is limited to a maximum of $70,000 per year.

Equity Compensation

Each non-employee Director will receive an initial stock option award and restricted stock unit award upon joining the Board and an annual stock option award and restricted stock unit award for each year of continued service as follows (subject to the aggregate grant date value limit described below):

Type of Grant	Number of Shares*
Initial Stock Option Grant	24,000
Initial Restricted Stock Unit Grant	10,667
Annual Stock Option Grant	12,000
Annual Restricted Stock Unit Grant	5,333

*These equity awards are to be automatically granted pursuant to the terms of the Ionis Pharmaceuticals, Inc. Amended and Restated 2002 Non-Employee Directors Stock Option Plan as approved by our stockholders on June 4, 2020 (the ***"NED Plan"***). Notwithstanding the terms of the NED Plan, the following annual equity compensation limits will apply to all non-employee Directors through May 24, 2026: (1) incumbent non-employee Directors will receive no more than $450,000 in annual equity compensation per year based on the aggregate grant date fair value (as determined in accordance with FASB Topic ASC 718 or its successor), and (2) newly appointed non-employee Directors will receive no more than $675,000 in initial equity compensation based on the aggregate grant date fair value (as determined in accordance with FASB Topic ASC 718 or its successor).

The exercise price of each stock option will be the Fair Market Value (as defined in the NED Plan) of Ionis' common stock on the date of grant.

As set forth in the NED Plan, one-third of the shares subject to stock options or restricted stock units for initial grants to new non-employee Directors vest on each annual anniversary of the date of grant and annual grants vest on either (1) the annual anniversary of the date of grant, or (2) the next regularly scheduled annual meeting of stockholders, whichever occurs earlier.

While serving on the Board, each non-employee Director may not sell Ionis shares obtained pursuant to vesting of restricted stock unit awards if selling such shares would reduce the shares owned by such non-employee Director (not including stock options or unvested restricted stock units) below an amount that is equal to five times his or her annual base cash retainer.

Review of Non-Employee Director Compensation Policy

This policy will be reviewed annually by Ionis' Compensation Committee and Board of Directors.

On at least an annual basis, Ionis will retain an independent consultant to (1) advise the Compensation Committee on recent developments and best practices concerning director compensation, and (2) compare Ionis' director compensation levels, policies, practices, and procedures to a set of peer companies selected by the Compensation Committee with input from the independent consultant.

Ionis reserves the right to amend this compensation policy at any time so long as the issuance of the equity awards comply with the terms of the NED Plan or any successor thereto.

Exhibit 10.2

IONIS PHARMACEUTICALS, INC.

AMENDED AND RESTATED

2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN

ADOPTED BY THE BOARD OF DIRECTORS SEPTEMBER 11, 2001
APPROVED BY STOCKHOLDERS MAY 31, 2002
EFFECTIVE DATE: MAY 31, 2002

AMENDED: APRIL 20, 2006 (Amendment approved by Board on December 12, 2005 and April 20, 2006 and by the Stockholders on May 3, 2006)

AMENDED: JUNE 5, 2008 (Amendment approved by Board on September 13, 2007 and February 22, 2008 and by the Stockholders on June 5, 2008)

AMENDED AND RESTATED: JUNE 2, 2010 (Amendment and Restatement approved by Board on February 26, 2010 and by the Stockholders on June 2, 2010)

AMENDED AND RESTATED: JUNE 7, 2012 (Amendment and Restatement approved by Board on March 27, 2012 and by the Stockholders on June 7, 2012)

AMENDED AND RESTATED: JUNE 10, 2014 (Amendment and Restatement approved by Board on February 11, 2014 and by the Stockholders on June 10, 2014)

AMENDED AND RESTATED: JUNE 30, 2015 (Amendment and Restatement approved by Board on March 20, 2015 and by the Stockholders on June 30, 2015)

AMENDED AND RESTATED: JUNE 4, 2020 (Amendment and Restatement approved by Board on March 24, 2020 and by the Stockholders on June 4, 2020)

AMENDED: MARCH 14, 2023

1. PURPOSES.

(a) Amendment and Restatement. This Plan was originally an amendment and restatement of the Ionis Pharmaceuticals, Inc. 1992 Non-Employee Directors' Stock Option Plan, and is an amendment of the Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan, as amended and restated on June 4, 2020.

(b) Eligible Recipients. The persons eligible to receive Stock Awards are the Non-Employee Directors of the Company.

(c) Available Stock Awards. The purpose of the Plan is to provide a means by which Non-Employee Directors may be given an opportunity to benefit from increases in value of the Common Stock through the granting of Stock Awards.

(d) General Purpose. The Company, by means of the Plan, seeks to retain the services of its Non-Employee Directors, to secure and retain the services of new Non-Employee Directors and to provide incentives for such persons to exert maximum efforts for the success of the Company and its Affiliates.

2. DEFINITIONS.

(a) ***"Affiliate"*** means any parent corporation or subsidiary corporation of the Company, whether now or hereafter existing, as those terms are defined in Sections 424(e) and (f), respectively, of the Code.

(b) ***"Annual Grant"*** means an Option and/or RSU Award granted annually to all Non-Employee Directors who meet the criteria specified in subsection 6(b) of the Plan.

(c) ***"Board"*** means the Board of Directors of the Company.

(d) ***"Capitalization Adjustment"*** has the meaning ascribed to that term in Section 12(a).

(e) ***"Change in Control"*** means the occurrence, in a single transaction or in a series of related transactions, of any one or more of the following events:

(i) any Exchange Act Person becomes the Owner, directly or indirectly, of securities of the Company representing more than 50% of the combined voting power of the Company's then outstanding securities other than by virtue of a merger, consolidation or similar transaction and other than by a purchase of securities directly from the Company;

Notwithstanding the foregoing, a Change in Control shall not be deemed to occur solely because the level of Ownership held by any Exchange Act Person (the "Subject Person") exceeds the percentage threshold specified above of the outstanding voting securities as a result of a repurchase or other acquisition of voting securities by the Company reducing the number of shares outstanding, *provided* that if a Change in Control would occur (but for the operation of this sentence) as a result of the acquisition of voting securities by the Company, and after such share acquisition, the Subject Person becomes the Owner of any additional voting securities (other than through a purchase directly from the Company) that, assuming the repurchase or other acquisition had not occurred, increases the percentage of the then outstanding voting securities Owned by the Subject Person over the percentage threshold specified above, then a Change in Control shall be deemed to occur.

(ii) there is consummated a merger, consolidation or similar transaction involving (directly or indirectly) the Company and, immediately after the consummation of such merger, consolidation or similar transaction, the stockholders of the Company immediately prior thereto do not Own, directly or indirectly, outstanding voting securities representing more than 50% of the combined outstanding voting power of the surviving Entity in such merger, consolidation or similar transaction or more than 50% of the combined outstanding voting power of the parent of the surviving Entity in such merger, consolidation or similar transaction;

(iii) the stockholders of the Company approve or the Board approves a plan of complete dissolution or liquidation of the Company, or a complete dissolution or liquidation of the Company shall otherwise occur;

(iv) there is consummated a sale, lease, license or other disposition of all or substantially all of the consolidated assets of the Company and its Subsidiaries, other than a sale, lease, license or other disposition of all or substantially all of the consolidated assets of the Company and its Subsidiaries to an Entity, more than 50% of the combined voting power of the voting securities of which are Owned by stockholders of the Company in substantially the same proportions as their Ownership of the Company immediately prior to such sale, lease, license or other disposition; or

(v) individuals who, on the date this Plan is adopted by the Board, are members of the Board (the "Incumbent Board") cease for any reason to constitute at least a majority of the members of the Board; (*provided, however,* that if the appointment or election (or nomination for election) of any new Board member was approved or recommended by a majority vote of the members of the Incumbent Board then still in office, such new member shall, for purposes of this Plan, be considered as a member of the Incumbent Board).

Notwithstanding the foregoing or any other provision of this Plan, the definition of Change in Control (or any analogous term) in an individual written agreement between the Company or any Affiliate and the Holder shall supersede the foregoing definition with respect to Stock Awards subject to such agreement (it being understood, however, that if no definition of Change in Control or any analogous term is set forth in such an individual written agreement, the foregoing definition shall apply).

(f) ***"Code"*** means the Internal Revenue Code of 1986, as amended.

(g) ***"Common Stock"*** means the common stock of the Company.

(h) ***"Company"*** means Ionis Pharmaceuticals, Inc., a Delaware corporation.

(i) ***"Consultant"*** means any person, including an advisor, (i) engaged by the Company or an Affiliate to render consulting or advisory services and who is compensated for such services or (ii) serving as a member of the Board of Directors of an Affiliate and who is compensated for such services. However, the term "Consultant" shall not include Directors who are not compensated by the Company for their services as Directors, and the payment of a director's fee by the Company for services as a Director shall not cause a Director to be considered a "Consultant" for purposes of the Plan.

(j) ***"Continuous Service"*** means that the Holder's service with the Company or an Affiliate, whether as an Employee, Director or Consultant, is not interrupted or terminated. A change in the capacity in which the Holder renders service to the Company or an Affiliate as an Employee, Consultant or Director or a change in the entity for which the Holder renders such service, provided that there is no interruption or termination of the Holder's service with the Company or an Affiliate, shall not terminate a Holder's Continuous Service. For example, a change in status from a Non-Employee Director of the Company to a Consultant of an Affiliate or an Employee of the Company shall not constitute an interruption of Continuous Service. The Board or the chief executive officer of the Company, in that party's sole discretion, may determine whether Continuous Service shall be considered interrupted in the case of any leave of absence approved by that party, including sick leave, military leave or any other personal leave.

(k) ***"Corporate Transaction"*** means the occurrence, in a single transaction or in a series of related transactions, of any one or more of the following events:

(i) a sale or other disposition of all or substantially all, as determined by the Board in its discretion, of the consolidated assets of the Company and its Subsidiaries;

(ii) a sale or other disposition of at least 90% of the outstanding securities of the Company;

(iii) a merger, consolidation or similar transaction following which the Company is not the surviving corporation; or

(iv) a merger, consolidation or similar transaction following which the Company is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger, consolidation or similar transaction are converted or exchanged by virtue of the merger, consolidation or similar transaction into other property, whether in the form of securities, cash or otherwise.

(l) ***"Director"*** means a member of the Board of Directors of the Company.

(m) ***"Disability"*** means the permanent and total disability of a person within the meaning of Section 22(e)(3) of the Code.

(n) ***"Employee"*** means any person employed by the Company or an Affiliate. Service as a Director or payment of a director's fee by the Company or an Affiliate shall not be sufficient to constitute "employment" by the Company or an Affiliate.

(o) ***"Entity"*** means a corporation, partnership or other entity.

(p) ***"Exchange Act"*** means the Securities Exchange Act of 1934, as amended.

(q) ***"Exchange Act Person"*** means any natural person, Entity or "group" (within the meaning of Section 13(d) or 14(d) of the Exchange Act), except that "Exchange Act Person" shall not include (A) the Company or any Subsidiary of the Company, (B) any employee benefit plan of the Company or any Subsidiary of the Company or any trustee or other fiduciary holding securities under an employee benefit plan of the Company or any Subsidiary of the Company, (C) an underwriter temporarily holding securities pursuant to an offering of such securities, or (D) an Entity Owned, directly or indirectly, by the stockholders of the Company in substantially the same proportions as their Ownership of stock of the Company.

(r) ***"Fair Market Value"*** means, as of any date, the value of the Common Stock determined as follows:

(i) If the Common Stock is listed on any established stock exchange or traded on the Nasdaq National Market or the Nasdaq SmallCap Market, the Fair Market Value of a share of Common Stock shall be the closing sales price for such stock (or the closing bid, if no sales were reported) as quoted on such exchange or market (or the exchange or market with the greatest volume of trading in the Common Stock) on the last market trading day prior to the day of determination, as reported in The Wall Street Journal or such other source as the Board deems reliable.

(ii) In the absence of such markets for the Common Stock, the Fair Market Value shall be determined in good faith by the Board.

(s) ***"Holder"*** means a person to whom an Option or RSU Award is granted pursuant to the Plan or, if applicable, such other person who holds an outstanding Option or RSU Award.

(t) ***"Initial Grant"*** means an Option and/or RSU granted to a Non-Employee Director who meets the criteria specified in subsection 6(a) of the Plan.

(u) ***"Non-Employee Director"*** means a Director who is not an Employee.

(v) ***"Nonstatutory Stock Option"*** means an Option not intended to qualify as an incentive stock option within the meaning of Section 422 of the Code and the regulations promulgated thereunder.

(w) ***"Officer"*** means a person who is an officer of the Company within the meaning of Section 16 of the Exchange Act and the rules and regulations promulgated thereunder.

(x) ***"Option"*** means a Nonstatutory Stock Option granted pursuant to the Plan.

(y) ***"Option Agreement"*** means a written agreement between the Company and a Holder evidencing the terms and conditions of an individual Option grant. Each Option Agreement shall be subject to the terms and conditions of the Plan.

(z) ***"Own," "Owned," "Owner," "Ownership"*** A person or Entity shall be deemed to "Own," to have "Owned," to be the "Owner" of, or to have acquired "Ownership" of securities if such person or Entity, directly or indirectly, through any contract, arrangement, understanding, relationship or otherwise, has or shares voting power, which includes the power to vote or to direct the voting, with respect to such securities.

(aa) ***"Plan"*** means this Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan, which is an amendment and restatement of the Ionis Pharmaceuticals, Inc. 1992 Non-Employee Directors' Stock Option Plan.

(bb) ***"RSU Award"*** means a right to receive shares of Common Stock which is granted pursuant to the terms and conditions of Section 8.

(cc) ***"RSU Award Agreement"*** means a written agreement between the Company and a holder of a RSU Award evidencing the terms and conditions of a RSU Award grant. Each RSU Award Agreement shall be subject to the terms and conditions of the Plan.

(dd) ***"Rule 16b-3"*** means Rule 16b-3 promulgated under the Exchange Act or any successor to Rule 16b-3, as in effect from time to time.

(ee) ***"Securities Act"*** means the Securities Act of 1933, as amended.

(ff) ***"Stock Award"*** means an Option or RSU Award, as applicable.

(gg) ***"Subsidiary"*** means, with respect to the Company, (i) any corporation of which more than 50% of the outstanding capital stock having ordinary voting power to elect a majority of the board of directors of such corporation (irrespective of whether, at the time, stock of any other class or classes of such corporation shall have or might have voting power by reason of the happening of any contingency) is at the time, directly or indirectly Owned by the Company, and (ii) any partnership in which the Company has a direct or indirect interest (whether in the form of voting or participation in profits or capital contribution) of more than 50%.

3. ADMINISTRATION.

(a) Administration by Board. The Board shall administer the Plan. The Board may delegate administration of the Plan to a committee. If delegated to a committee, references to the Board will include a reference to the committee, as applicable.

(b) Powers of Board. The Board shall have the power, subject to, and within the limitations of, the express provisions of the Plan:

(i) To determine the provisions of each Stock Award to the extent not specified in the Plan.

(ii) To construe and interpret the Plan and Stock Awards granted under it, and to establish, amend and revoke rules and regulations for its administration. The Board, in the exercise of this power, may correct any defect, omission or inconsistency in the Plan or in any Option Agreement or RSU Agreement, in a manner and to the extent it shall deem necessary or expedient to make the Plan fully effective.

(iii) To amend the Plan or a Stock Award as provided in Section 13.

(iv) To terminate or suspend the Plan as provided in Section 14.

(v) Generally, to exercise such powers and to perform such acts as the Board deems necessary or expedient to promote the best interests of the Company and that are not in conflict with the provisions of the Plan.

(c) Effect of Board's Decision. All determinations, interpretations and constructions made by the Board in good faith shall not be subject to review by any person and shall be final, binding and conclusive on all persons.

(d) Arbitration. Any dispute or claim concerning any Stock Award granted (or not granted) pursuant to the Plan or any disputes or claims relating to or arising out of the Plan shall be fully, finally and exclusively resolved by binding arbitration conducted pursuant to the Commercial Arbitration Rules of the American Arbitration Association in San Diego, California. The Company shall pay all arbitration fees. In addition to any other relief, the arbitrator may award to the prevailing party recovery of its attorney's fees and costs. By accepting a Stock Award, Holders and the Company waive their respective rights to have any such disputes or claims tried by a judge or jury.

4. SHARES SUBJECT TO THE PLAN.

(a) Share Reserve. Subject to the provisions of Section 12(a) relating to Capitalization Adjustments, the Common Stock that may be issued pursuant to Stock Awards shall not exceed in the aggregate **2,800,000** shares of Common Stock.

(b) Reversion of Shares to the Share Reserve. If any Stock Award shall for any reason expire or otherwise terminate, in whole or in part, without having been exercised or vested in full, the shares of Common Stock not issued under such Stock Award shall revert to and again become available for issuance under the Plan.

(c) Source of Shares. The shares of Common Stock subject to the Plan may be unissued shares or reacquired shares, bought on the market or otherwise.

5. ELIGIBILITY.

The Stock Awards as set forth in Section 6 of the Plan automatically shall be granted under the Plan to all Non-Employee Directors.

6. NON-DISCRETIONARY GRANTS.

(a) Initial Grants. Without any further action of the Board, each person who is elected or appointed for the first time to be a Non-Employee Director shall automatically be granted, on the terms and conditions set forth herein, an Initial Grant of Option and RSU Awards as follows:

(i) An Option to purchase 24,000 shares of Common Stock; and

(ii) An RSU Award of 10,667 RSUs.

(iii) The grant date for such initial options will be the date the Non-Employee Director was elected or appointed by the Board or stockholders of the Company, as applicable. The grant date for such initial RSU Awards will be the 15th of the month following the end of the quarter in which such Non-Employee Director was elected or appointed by the Board or stockholders of the Company, as applicable.

(b) Annual Grants. Without any further action of the Board, a Non-Employee Director shall be granted an Annual Grant as follows: On July 1 of each year, beginning on July 1, 2020, each person who is then a Non-Employee Director automatically shall be granted, on the terms and conditions set forth herein, an Annual Grant of Option and RSU Awards as follows:

(i) An Option to purchase 12,000 shares of Common Stock; and

(ii) An RSU Award of 5,333 RSUs.

7. OPTION PROVISIONS.

Each Option shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. Each Option shall include (through incorporation of provisions hereof by reference in the Option or otherwise) the substance of each of the following provisions:

(a) Term. No Option shall be exercisable after the expiration of 10 years from the date it was granted.

(b) Exercise Price. The exercise price of each Option shall be 100% of the Fair Market Value of the Common Stock subject to the Option on the date the Option is granted. Notwithstanding the foregoing, an Option may be granted with an exercise price lower than that set forth in the preceding sentence if such Option is granted pursuant to an assumption or substitution for another option in a manner satisfying the provisions of Section 424(a) of the Code.

(c) Consideration. The purchase price of Common Stock acquired pursuant to the exercise of an Option shall be paid, to the extent permitted by applicable law, by any combination of the following methods of payment:

(i) by cash, check, bank draft or money order payable to the Company; or

(ii) pursuant to a program developed under Regulation T as promulgated by the Federal Reserve Board that, prior to the issuance of the stock subject to the Option, results in either the receipt of cash (or check) by the Company or the receipt of irrevocable instructions to pay the aggregate exercise price to the Company from the sales proceeds.

(d) Transferability. An Option will not be transferable except as determined by the Board.

(e) Exercise Schedule. The Option shall be exercisable as the shares of Common Stock subject to the Option vest.

(f) Vesting Schedule. The Option shall vest and become exercisable as follows:

(i) Initial Grants: one-third of the shares subject to the Option shall vest on each annual anniversary of the date of grant, provided that the Holder has, during the entire year prior to each vesting date, continuously served as a Non-Employee Director or as an Employee of or Consultant to the Company or any Affiliate, whereupon such option shall become fully exercisable in accordance with its terms with respect to that portion of the shares represented by that installment.

(ii) Annual Grants: 100% of the shares subject to the Option shall vest on (1) the annual anniversary of the date of grant, or (2) the next regularly scheduled annual meeting of stockholders, whichever occurs earlier, provided that the Holder has, during the entire period from the date of grant through such vesting date, continuously served as a Non-Employee Director or as an Employee of or Consultant to the Company or any Affiliate, whereupon such option shall become fully exercisable in accordance with its terms.

(g) Termination of Continuous Service. In the event that an Holder's Continuous Service terminates (other than upon the Holder's death or Disability), the Holder may exercise his or her Option (to the extent that the Holder was entitled to exercise such Option as of the date of termination) but only within such period of time ending on the earlier of (i) the date 3 months following the termination of the Holder's Continuous Service (or such longer or shorter period specified in the Option Agreement), or (ii) the expiration of the term of the Option as set forth in the Option Agreement. If, after termination, the Holder does not exercise his or her Option within the time specified in the Option Agreement, the Option shall terminate.

(h) Extension of Termination Date. An Holder's Option Agreement may also provide that if the exercise of the Option following the termination of the Holder's Continuous Service (other than upon the Holder's death or Disability) would be prohibited at any time solely because the issuance of shares of Common Stock would violate the registration requirements under the Securities Act, then the Option shall terminate on the earlier of (i) the expiration of the term of the Option set forth in subsection 7(a) or (ii) the expiration of a period of 3 months after the termination of the Holder's Continuous Service during which the exercise of the Option would not be in violation of such registration requirements. In addition, unless otherwise provided in an Holder's Option Agreement, if the immediate sale of any Common Stock received upon exercise of an Option following the termination of the Holder's Continuous Service would violate the Company's insider trading policy, then the Option shall terminate on the earlier of (i) the expiration of a period equal to the applicable post-termination exercise period after the termination of the Holder's Continuous Service during which the sale of Common Stock received upon exercise of the Option would not be in violation of the Company's insider trading policy, or (ii) the expiration of the term of the Option as set forth in the applicable Option Agreement.

(i) Disability of Holder. In the event that an Holder's Continuous Service terminates as a result of the Holder's Disability, the Holder may exercise his or her Option (to the extent that the Holder was entitled to exercise such Option as of the date of termination), but only within such period of time ending on the earlier of (i) the date 12 months following such termination (or such longer or shorter period specified in the Option Agreement) or (ii) the expiration of the term of the Option as set forth in the Option Agreement. If, after termination, the Holder does not exercise his or her Option within the time specified herein, the Option shall terminate.

(j) Death of Holder. In the event that (i) an Holder's Continuous Service terminates as a result of the Holder's death or (ii) the Holder dies within the period (if any) specified in the Option Agreement after the termination of the Holder's Continuous Service for a reason other than death, then the Option may be exercised (to the extent the Holder was entitled to exercise such Option as of the date of death) by the Holder's estate, by a person who acquired the right to exercise the Option by bequest or inheritance or by a person designated to exercise the Option upon the Holder's death pursuant to subsection 7(d), but only within the period ending on the earlier of (1) the date 18 months following the date of death (or such longer or shorter period specified in the Option Agreement) or (2) the expiration of the term of such Option as set forth in the Option Agreement. If, after death, the Option is not exercised within the time specified herein, the Option shall terminate.

8. Restricted Stock Unit Provisions.

Each Restricted Stock Unit Award Agreement shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. The terms and conditions of Restricted Stock Unit Award Agreements may change from time to time, and the terms and conditions of separate Restricted Stock Unit Award Agreements need not be identical; *provided*, *however*, that each Restricted Stock Unit Award Agreement shall conform to (through incorporation of the provisions hereof by reference in the Agreement or otherwise) the substance of each of the following provisions:

(a) Consideration. At the time of grant of a Restricted Stock Unit Award, the Board will determine the consideration, if any, to be paid by the Holder upon delivery of each share of Common Stock subject to the Restricted Stock Unit Award. The consideration to be paid (if any) by the Holder for each share of Common Stock subject to a Restricted Stock Unit Award may be paid in any form of legal consideration that may be acceptable to the Board, in its sole discretion, and permissible under applicable law.

(b) Vesting. Each RSU Award under this Plan shall vest as follows:

(i) Initial Grants: one-third of the shares subject to the RSU shall vest on each annual anniversary of the date of grant, provided that the Holder has, during the entire year prior to each vesting date, continuously served as a Non-Employee Director or as an Employee of or Consultant to the Company or any Affiliate.

(ii) Annual Grants: 100% of the shares subject to the RSU shall vest on (1) the annual anniversary of the date of grant, or (2) the next regularly scheduled annual meeting of stockholders, whichever occurs earlier, provided that the Holder has, during the entire period from the date of grant through such vesting date, continuously served as a Non-Employee Director or as an Employee of or Consultant to the Company or any Affiliate; provided such RSU Awards, once vested, will be settled on the July 15th following the vesting date.

(c) Payment. A Restricted Stock Unit Award may be settled by the delivery of shares of Common Stock, their cash equivalent, any combination thereof or in any other form of consideration, as determined by the Board and contained in the Restricted Stock Unit Award Agreement.

(d) Additional Restrictions. At the time of the grant of a Restricted Stock Unit Award, the Board, as it deems appropriate, may impose such restrictions or conditions that delay the delivery of the shares of Common Stock (or their cash equivalent) subject to a Restricted Stock Unit Award to a time after the vesting of such Restricted Stock Unit Award.

(e) Dividend Equivalents. Dividend equivalents may be credited in respect of shares of Common Stock covered by a Restricted Stock Unit Award, as determined by the Board and contained in the Restricted Stock Unit Award Agreement. At the sole discretion of the Board, such dividend equivalents may be converted into additional shares of Common Stock covered by the Restricted Stock Unit Award in such manner as determined by the Board. Any additional shares covered by the Restricted Stock Unit Award credited by reason of such dividend equivalents will be subject to all of the same terms and conditions of the underlying Restricted Stock Unit Award Agreement to which they relate.

(f) Termination of Holder's Continuous Service. Except as otherwise provided in the applicable Restricted Stock Unit Award Agreement, such portion of the Restricted Stock Unit Award that has not vested will be forfeited upon the Holder's termination of Continuous Service.

9. COVENANTS OF THE COMPANY.

(a) Availability of Shares. During the terms of the Stock Awards, the Company shall keep available at all times the number of shares of Common Stock required to satisfy such Stock Awards.

(b) Securities Law Compliance. The Company shall seek to obtain from each regulatory commission or agency having jurisdiction over the Plan such authority as may be required to grant Stock Awards and to issue and sell shares of Common Stock upon exercise of the Stock Awards; provided, however, that this undertaking shall not require the Company to register under the Securities Act the Plan, any Stock Award or any Common Stock issued or issuable pursuant to any such Stock Award. If, after reasonable efforts, the Company is unable to obtain from any such regulatory commission or agency the authority which counsel for the Company deems necessary for the lawful issuance and sale of Common Stock under the Plan, the Company shall be relieved from any liability for failure to issue and sell Common Stock upon exercise of such Stock Awards unless and until such authority is obtained. A Non-Employee Director shall not be eligible for the grant of a Stock Award or the subsequent issuance of Common Stock pursuant to the Stock Award if such grant or issuance would violate any applicable securities law.

(c) No Obligation to Notify or Minimize Taxes. The Company shall have no duty or obligation to any Holder to advise such Holder (or the estate of, or transferee of, such Holder) as to the time or manner of exercising such Stock Award. Furthermore, the Company shall have no duty or obligation to warn or otherwise advise such Holder (or the estate of, or transferee of, such Holder) of a pending termination or expiration of a Stock Award or a possible period in which the Stock Award may not be exercised. The Company has no duty or obligation to minimize the tax consequences of a Stock Award to the Holder of such Stock Award.

10. USE OF PROCEEDS FROM STOCK.

Proceeds from the sale of Common Stock pursuant to Options or RSU Awards (if any) shall constitute general funds of the Company.

11. MISCELLANEOUS.

(a) Acceleration of Exercisability and Vesting. The Board shall have the power to accelerate the time at which a Stock Award may first be exercised or the time during which a Stock Award or any part thereof will vest in accordance with the Plan, notwithstanding the provisions in the Stock Award stating the time at which it may first be exercised or the time during which it will vest.

(b) Stockholder Rights. No Holder shall be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares of Common Stock subject to such Stock Award unless and until such Holder has satisfied all requirements for exercise of the Option or settlement of the RSU Award, as applicable, pursuant to its terms.

(c) No Service Rights. Nothing in the Plan or any instrument executed or Stock Award granted pursuant thereto shall confer upon any Holder any right to continue to serve the Company as a Non-Employee Director or shall affect the right of the Company or an Affiliate to terminate (i) the employment of an Employee with or without notice and with or without cause, (ii) the service of a Consultant pursuant to the terms of such Consultant's agreement with the Company or an Affiliate or (iii) the service of a Director pursuant to the Bylaws of the Company or an Affiliate, and any applicable provisions of the corporate law of the state in which the Company or the Affiliate is incorporated, as the case may be.

(d) Investment Assurances. The Company may require a Holder, as a condition of exercising or acquiring Common Stock under any Award, (i) to give written assurances satisfactory to the Company as to the Holder's knowledge and experience in financial and business matters and/or to employ a purchaser representative reasonably satisfactory to the Company who is knowledgeable and experienced in financial and business matters and that he or she is capable of evaluating, alone or together with the purchaser representative, the merits and risks of exercising the Stock Award; and (ii) to give written assurances satisfactory to the Company stating that the Holder is acquiring the Common Stock subject to the Stock Award for the Holder's own account and not with any present intention of selling or otherwise distributing the Common Stock. The foregoing requirements, and any assurances given pursuant to such requirements, shall be inoperative if (1) the issuance of the shares of Common Stock upon the exercise or acquisition of Common Stock under the Stock Award has been registered under a then currently effective registration statement under the Securities Act or (2) as to any particular requirement, a determination is made by counsel for the Company that such requirement need not be met in the circumstances under the then applicable securities laws. The Company may, upon advice of counsel to the Company, place legends on stock certificates issued under the Plan as such counsel deems necessary or appropriate in order to comply with applicable securities laws, including, but not limited to, legends restricting the transfer of the Common Stock.

(e) Withholding Obligations. To the extent provided by the terms of the applicable Option Agreement or RSU Award Agreement, the Holder may satisfy any federal, state or local tax withholding obligation relating to the exercise or acquisition of Common Stock under a Stock Award by any of the following means (in addition to the Company's right to withhold from any compensation paid to the Holder by the Company) or by a combination of such means: (i) tendering a cash payment; (ii) authorizing the Company to withhold shares of Common Stock from the shares of Common Stock otherwise issuable to the Holder as a result of the exercise or acquisition of Common Stock under the Stock Award, *provided*, *however*, that no shares of Common Stock are withheld with a value exceeding the minimum amount of tax required to be withheld by law (or such lower amount as may be necessary to avoid variable award accounting); or (iii) delivering to the Company owned and unencumbered shares of Common Stock.

(f) Electronic Delivery. Any reference herein to a "written" agreement or document shall include any agreement or document delivered electronically or posted on the Company's intranet (or other shared electronic medium controlled by the Company to which the Holder has access).

12. Adjustments upon Changes in Stock.

(a) Capitalization Adjustments. If any change is made in, or other event occurs with respect to, the Common Stock subject to the Plan, or subject to any Stock Award, without the receipt of consideration by the Company (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by the Company) (each, a "Capitalization Adjustment"), the Plan will be appropriately adjusted in the class(es) and maximum number of securities subject both to the Plan pursuant to subsection 4(a) and to the nondiscretionary Stock Awards specified in Section 6, and the outstanding Stock Awards will be appropriately adjusted in the class(es) and number of securities and price per share of Common Stock subject to such outstanding Stock Awards. The Board shall make such adjustments, and its determination shall be final, binding and conclusive. (The conversion of any convertible securities of the Company shall not be treated as a transaction "without receipt of consideration" by the Company.)

(b) Dissolution or Liquidation. In the event of a dissolution or liquidation of the Company, then all outstanding Stock Awards shall terminate immediately prior to the completion of such dissolution or liquidation.

(c) Corporate Transaction. In the event of a Corporate Transaction, any surviving corporation or acquiring corporation may assume any or all Stock Awards outstanding under the Plan or may substitute similar stock awards for Stock Awards outstanding under the Plan (it being understood that similar stock awards include, but are not limited to, options to acquire, or restricted stock unit rights to receive, the same consideration paid to the stockholders or the Company, as the case may be, pursuant to the Corporate Transaction). In the event that any surviving corporation or acquiring corporation does not assume any or all such outstanding Stock Awards or substitute similar stock awards for such outstanding Stock Awards, then with respect to Stock Awards that have been neither assumed nor substituted and that are held by Holders whose Continuous Service has not terminated prior to the effective time of the Corporate Transaction, the vesting of such Stock Awards (and, if applicable, the time at which such Stock Awards may be exercised) shall (contingent upon the effectiveness of the Corporate Transaction) be accelerated in full to a date prior to the effective time of such Corporate Transaction as the Board shall determine (or, if the Board shall not determine such a date, to the date that is 5 days prior to the effective time of the Corporate Transaction), and the Stock Awards shall terminate if not exercised at or prior to such effective time. With respect to Stock Awards outstanding under the Plan that have been neither assumed nor substituted and that are held by Holders whose Continuous Service has terminated prior to the effective time of the Corporate Transaction, the vesting of such Stock Awards (and, if applicable, the time at which such Stock Award may be exercised) shall not be accelerated unless otherwise provided in a written agreement between the Company or any Affiliate and the holder of such Stock Award, and such Stock Awards shall terminate if not exercised prior to the effective time of the Corporate Transaction.

(d) Change in Control. Notwithstanding any other provisions of the Plan to the contrary, if a Change in Control occurs and the Holder's Continuous Service has not terminated prior to the effective date of such Change in Control, then the vesting and exercisability of the shares of Common Stock subject to the Holder's Stock Awards shall be accelerated in full as of the effective date of the Change in Control. Following such Change in Control (other than a Change in Control resulting from a plan of complete dissolution or liquidation of the Company) and notwithstanding any other provision of the Plan to the contrary and provided that the Holder's Continuous Service has not terminated prior to the effective date of the Change in Control, then the Holder's Options shall expire on the earliest of (i) 12 months following the effective date of such Change in Control or (ii) the Expiration Date indicated in the Holder's Grant Notice.

(e) Parachute Payments. If any payment or benefit the Holder would receive pursuant to a Change in Control from the Company or otherwise ("Payment") would (i) constitute a "parachute payment" within the meaning of Section 280G of the Code, and (ii) but for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the "Excise Tax"), then such Payment shall be reduced to the Reduced Amount. The "Reduced Amount" shall be either (x) the largest portion of the Payment that would result in no portion of the Payment being subject to the Excise Tax or (y) the largest portion, up to and including the total, of the Payment, whichever amount, after taking into account all applicable federal, state and local employment taxes, income taxes, and the Excise Tax (all computed at the highest applicable marginal rate), results in the Holder's receipt, on an after-tax basis, of the greater amount of the Payment notwithstanding that all or some portion of the Payment may be subject to the Excise Tax. If a reduction in a Payment is required pursuant to the preceding sentence and the Reduced Amount is determined pursuant to clause (x) of the preceding sentence, the reduction shall occur in the manner (the "***Reduction Method***") that results in the greatest economic benefit for Holder. If more than one method of reduction will result in the same economic benefit, the items so reduced will be reduced pro rata (the "***Pro Rata Reduction Method***"). Notwithstanding the foregoing, if the Reduction Method or the Pro Rata Reduction Method would result in any portion of the Payment being subject to taxes pursuant to Section 409A of the Code that would not otherwise be subject to taxes pursuant to Section 409A of the Code, then the Reduction Method and/or the Pro Rata Reduction Method, as the case may be, shall be modified so as to avoid the imposition of taxes pursuant to Section 409A of the Code as follows: (A) as a first priority, the modification shall preserve to the greatest extent possible, the greatest economic benefit for Holder as determined on an after-tax basis; (B) as a second priority, Payments that are contingent on future events (e.g., being terminated without cause), shall be reduced (or eliminated) before Payments that are not contingent on future events; and (C) as a third priority, Payments that are "deferred compensation" within the meaning of Section 409A of the Code shall be reduced (or eliminated) before Payments that are not deferred compensation within the meaning of Section 409A of the Code.

The accounting firm engaged by the Company for general audit purposes as of the day prior to the effective date of the Change in Control shall perform the foregoing calculations. If the accounting firm so engaged by the Company is serving as accountant or auditor for the individual, entity or group effecting the Change in Control, the Company shall appoint a nationally recognized accounting firm to make the determinations required hereunder. The Company shall bear all expenses with respect to the determinations by such accounting firm required to be made hereunder.

The accounting firm engaged to make the determinations hereunder shall provide its calculations, together with detailed supporting documentation, to the Holder and the Company within 15 calendar days after the date on which the Holder's right to a Payment is triggered (if requested at that time by the Holder or the Company) or such other time as requested by the Holder or the Company. If the accounting firm determines that no Excise Tax is payable with respect to a Payment, either before or after the application of the Reduced Amount, it shall furnish the Company and the Holder with an opinion reasonably acceptable to the Holder that no Excise Tax will be imposed with respect to such Payment. Any good faith determinations of the accounting firm made hereunder shall be final, binding and conclusive upon the Holder and the Company.

13. AMENDMENT OF THE PLAN AND STOCK AWARDS.

(a) Amendment of Plan. The Board at any time, and from time to time, may amend the Plan. However, except as provided in Section 12(a) relating to Capitalization Adjustments, no amendment shall be effective unless approved by the stockholders of the Company to the extent stockholder approval is necessary to satisfy the requirements of Rule 16b-3 or any Nasdaq or securities exchange listing requirements.

(b) Stockholder Approval. The Board, in its sole discretion, may submit any other amendment to the Plan for stockholder approval.

(c) No Impairment of Rights. Rights under any Stock Award granted before amendment of the Plan shall not be impaired by any amendment of the Plan unless (i) the Company requests the consent of the Holder and (ii) the Holder consents in writing.

(d) Amendment of Stock Awards. The Board at any time, and from time to time, may amend the terms of any one or more Stock Awards; *provided*, *however*, that the rights under any Stock Award shall not be impaired by any such amendment unless (i) the Company requests the consent of the Holder and (ii) the Holder consents in writing.

(e) Prohibition on Reduction of Exercise Prices, Cancellation and Re-Grant of Stock Awards. Neither the Board nor any Committee (or subcommittee) shall have the authority to: (i) reduce the exercise price of any outstanding Options under the Plan, or (ii) cancel any outstanding Options that have an exercise price or strike price greater than the current Fair Market Value of the Common Stock in exchange for cash or other Stock Awards under the Plan, unless the stockholders of the Company have approved such an action within 12 months prior to such an event. Notwithstanding the foregoing, this paragraph will not be construed to apply to "issuing or assuming a stock option in a transaction to which section 424(a) applies," within the meaning of Section 424 of the Code."

14. Termination or Suspension of the Plan.

(a) Plan Term. The Board may suspend or terminate the Plan at any time. Unless sooner terminated, the Plan shall terminate on June 1, 2030. No Stock Awards may be granted under the Plan while the Plan is suspended or after it is terminated.

(b) No Impairment of Rights. Suspension or termination of the Plan shall not impair rights and obligations under any Stock Award granted while the Plan is in effect except with the written consent of the Holder.

15. Effective Date of Plan.

The Plan shall become effective as determined by the Board, but no Stock Award shall be exercised unless and until the Plan has been approved by the stockholders of the Company, which approval shall be within 12 months before or after the date the Plan is adopted by the Board.

16. Choice of Law.

The law of the State of California shall govern all questions concerning the construction, validity and interpretation of this Plan without regard to such state's conflict of laws rules.

Exhibit 10.3

IONIS PHARMACEUTICALS, INC.
RESTRICTED STOCK UNIT GRANT NOTICE
(AMENDED & RESTATED 2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN)

Ionis Pharmaceuticals, Inc. (the ***"Company"***), pursuant to its Amended & Restated 2002 Non-Employee Directors' Stock Option Plan (the ***"Plan"***), hereby awards to Participant a Restricted Stock Unit Award for the number of stock units set forth below (the ***"Award"***). The Award is subject to all of the terms and conditions as set forth herein; and in the Plan and the Restricted Stock Unit Agreement, both of which are attached hereto and incorporated herein in their entirety. Capitalized terms not otherwise defined herein shall have the meanings set forth in the Plan or the Restricted Stock Unit Agreement. In the event of any conflict between the terms in the Award and the Plan, the terms of the Plan shall control.

Participant:	
Date of Grant:	
Delivery Date:	
Number of Stock Units Subject to Award:	
Consideration:	Participant's Services

Vesting Schedule: 100% of the Stock Units subject to this Award will vest either on (1) the annual anniversary of the Date of Grant, or (2) the next regularly scheduled annual meeting of stockholders of the Company, whichever occurs earlier. Notwithstanding the foregoing, vesting shall terminate upon the Participant's termination of Continuous Service.

Issuance Schedule: The shares of Common Stock to be issued in respect of the Award will be issued in accordance with the issuance schedule set forth in Section 6 of the Restricted Stock Unit Agreement.

Additional Terms/Acknowledgements: The undersigned Participant acknowledges receipt of, and understands and agrees to, this Restricted Stock Unit Grant Notice, the Restricted Stock Unit Agreement and the Plan. Participant further acknowledges that as of the Date of Grant, this Restricted Stock Unit Grant Notice, the Restricted Stock Unit Agreement and the Plan set forth the entire understanding between Participant and the Company regarding the Award and supersedes all prior oral and written agreements on that subject.

IONIS PHARMACEUTICALS, INC.	**PARTICIPANT:**
By: _____	_____
Signature	Signature
Title: _____	Date: _____
Date: _____	

ATTACHMENTS: Restricted Stock Unit Agreement, Amended & Restated 2002 Non-Employee Directors' Stock Option Plan

IONIS PHARMACEUTICALS, INC.
RESTRICTED STOCK UNIT GRANT NOTICE
FOR DEFERRED RESTRICTED STOCK UNITS
(AMENDED & RESTATED 2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN)

Ionis Pharmaceuticals, Inc. (the ***"Company"***), pursuant to its Amended & Restated 2002 Non-Employee Directors' Stock Option Plan (the ***"Plan"***), hereby awards to Participant a Restricted Stock Unit Award for the number of Stock Units set forth below (the ***"Award"***). The Award is subject to all of the terms and conditions as set forth herein; and in the Plan and the Restricted Stock Unit Agreement (the "***RSU Agreement***"), both of which are attached hereto and incorporated herein in their entirety. Capitalized terms not otherwise defined herein shall have the meanings set forth in the Plan or the RSU Agreement. In the event of any conflict between the terms in the Award and the Plan, the terms of the Plan shall control.

Participant:	«Name»
Date of Grant:	«Date»
Vesting Commencement Date:	«Date»
Number of Stock Units Subject to Award:	«Shares»
Consideration:	Participant's Services

Vesting Schedule: 100% of the Stock Units subject to this Award will vest either on (1) the annual anniversary of the Date of Grant, or (2) the next regularly scheduled annual meeting of stockholders of the Company, whichever occurs earlier. Notwithstanding the foregoing, vesting shall terminate upon the Participant's termination of Continuous Service.

Issuance Schedule: Subject to Sections 6 and 19 of the RSU Agreement, and subject to any Capitalization Adjustment, one share of Common Stock (or its cash equivalent, at the discretion of the Company) will be issued for each Stock Unit that has vested under this Award on the first to occur of the following as indicated by the check mark below (such date, the "***Settlement Date***"):

☐ **DEFERRAL CHOICE A**:

- The fifth anniversary of the vesting date;
- The thirtieth (30th) day following the Participant's "separation from service" (as defined under Treasury Regulation Section 1.409A-1(h), without regard to any alternative definitions therein, a "***Separation from Service***"); or
- The date of a change in control of the Company that also would constitute a "change in control event" (as defined under Treasury Regulation Section 1.409A-3(i)(5), a "***409A Change in Control***").

☐ **DEFERRAL CHOICE B:**

- The thirtieth (30th) day following the Participant's Separation from Service; or
- The date of a 409A Change in Control.

Additional Terms/Acknowledgements: The undersigned Participant acknowledges receipt of, and understands and agrees to, this Restricted Stock Unit Grant Notice, the RSU Agreement, and the Plan. Participant further acknowledges that as of the Date of Grant, this Restricted Stock Unit Grant Notice, the RSU Agreement, and the Plan set forth the entire understanding between Participant and the Company regarding the Award and supersedes all prior oral and written agreements on that subject.

IONIS PHARMACEUTICALS, INC.

By: _____
Signature

Title: EVP Finance & CFO

Date: _____

PARTICIPANT:

_____
Signature

Date: _____

ATTACHMENTS: Restricted Stock Unit Agreement, Amended & Restated 2002 Non-Employee Directors' Stock Option Plan

IONIS PHARMACEUTICALS, INC.
AMENDED & RESTATED 2002 NON-EMPLOYEE DIRECTORS'
STOCK OPTION PLAN

RESTRICTED STOCK UNIT AGREEMENT

Pursuant to the Restricted Stock Unit Grant Notice ("***Grant Notice***") and this Restricted Stock Unit Agreement and in consideration of your services, Ionis Pharmaceuticals, Inc. (the "***Company***") has awarded you a Restricted Stock Unit Award (the "***Award***") under its Amended & Restated 2002 Non-Employee Director's Stock Option Plan (the "***Plan***"). Your Award is granted to you effective as of the Date of Grant set forth in the Grant Notice for this Award. This Restricted Stock Unit Agreement shall be deemed to be agreed to by the Company and you upon the earlier of (i) signing (or electronic acceptance) by you of the Restricted Stock Unit Grant Notice to which it is attached, and (ii) your receipt of shares of Common Stock under this Restricted Stock Unit Agreement. Capitalized terms not explicitly defined in this Restricted Stock Unit Agreement shall have the same meanings given to them in the Plan or the Grant Notice, as applicable. In the event of any conflict between the terms in this Restricted Stock Unit Agreement and the Plan, the terms of the Plan shall control. The details of your Award, in addition to those set forth in the Grant Notice and the Plan, are as follows.

1. GRANT OF THE AWARD. This Award represents the right to be issued on a future date the number of shares of the Company's Common Stock that is equal to the number of stock units indicated in the Grant Notice (the "***Stock Units***"). As of the Date of Grant, the Company will credit to a bookkeeping account maintained by the Company for your benefit (the "***Account***") the number of Stock Units subject to the Award. This Award was granted in consideration of your services to the Company. Except as otherwise provided herein, you will not be required to make any payment to the Company (other than past and future services to the Company) with respect to your receipt of the Award, the vesting of the Stock Units or the delivery of the Common Stock to be issued in respect of the Award.

2. VESTING.

(a) In General. Subject to the limitations contained herein, your Award will vest, if at all, in accordance with the vesting schedule provided in the Grant Notice, provided that vesting will cease upon the termination of your Continuous Service. Upon such termination of your Continuous Service, the Stock Units credited to the Account that were not vested on the date of such termination will be forfeited at no cost to the Company and you will have no further right, title or interest in the Stock Units or the shares of Common Stock to be issued in respect of the Award.

3. NUMBER OF SHARES.

(a) The number of Stock Units subject to your Award may be adjusted from time to time for Capitalization Adjustments, as provided in the Plan.

(b) Any additional Stock Units that become subject to the Award pursuant to this Section 3 and Section 7, if any, shall be subject, in a manner determined by the Board, to the same forfeiture restrictions, restrictions on transferability, and time and manner of delivery as applicable to the other Stock Units covered by your Award.

(c) Notwithstanding the provisions of this Section 3, no fractional shares or rights for fractional shares of Common Stock shall be created pursuant to this Section 3. The Board shall, in its discretion, determine an equivalent benefit for any fractional shares or fractional shares that might be created by the adjustments referred to in this Section 3.

4. Securities Law Compliance. You may not be issued any shares in respect of your Award unless either (i) the shares are registered under the Securities Act; or (ii) the Company has determined that such issuance would be exempt from the registration requirements of the Securities Act. Your Award also must comply with other applicable laws and regulations governing the Award, and you will not receive such shares if the Company determines that such receipt would not be in material compliance with such laws and regulations.

5. Transfer Restrictions. Prior to the time that shares of Common Stock have been delivered to you, you may not transfer, pledge, sell or otherwise dispose of this Award or the shares issuable in respect of your Award, except as expressly provided in this Section 5. For example, you may not use shares that may be issued in respect of your Award as security for a loan. The restrictions on transfer set forth herein will lapse upon delivery to you of shares in respect of your vested Award.

(a) Death. Your Award is transferable by will and by the laws of descent and distribution. In addition, upon receiving written permission from the Board or its duly authorized designee, you may, by delivering written notice to the Company, in a form provided by or otherwise satisfactory to the Company and any broker designated by the Company to effect transactions under the Plan, designate a third party who, in the event of your death, shall thereafter be entitled to receive any distribution of Common Stock or other consideration to which you were entitled at the time of your death pursuant to this Agreement. In the absence of such a designation, your executor or administrator of your estate shall be entitled to receive, on behalf of your estate, such Common Stock or other consideration.

(b) Certain Trusts. Upon receiving written permission from the Board or its duly authorized designee, you may transfer your Award to a trust if you are considered to be the sole beneficial owner (determined under Section 671 of the Code and applicable state law) while the Award is held in the trust, provided that you and the trustee enter into transfer and other agreements required by the Company.

(c) Domestic Relations Orders. Upon receiving written permission from the Board or its duly authorized designee, and provided that you and the designated transferee enter into transfer and other agreements required by the Company, you may transfer your Award or your right to receive the distribution of Common Stock or other consideration thereunder, pursuant to a domestic relations order that contains the information required by the Company to effectuate the transfer. You are encouraged to discuss the proposed terms of any division of this Award with the Company prior to finalizing the domestic relations order to help ensure the required information is contained within the domestic relations order.

6. Date of Issuance. In the event that one or more Stock Units vests, subject to the satisfaction of the Withholding Obligation set forth in Section 10, the Company will issue to you one share of Common Stock for each vested Stock Unit on the Settlement Date determined under the Grant Notice, but in all cases, except as may be required by Section 19, not later than December 31 of the calendar year in which the Settlement Date occurs. If a scheduled delivery date falls on a date that is not a business day, such delivery date shall instead fall on the next following business day.

7. Dividends. You shall be entitled to receive payments equal to any cash dividends and other distributions paid with respect to a corresponding number of shares to be issued in respect of the Stock Units covered by your Award, provided that if any such dividends or distributions are paid in shares, the Fair Market Value of such shares shall be converted into additional Stock Units covered by the Award, and further provided that such additional Stock Units shall be subject to the same forfeiture restrictions and restrictions on transferability as apply to the Stock Units subject to the Award with respect to which they relate.

8. Restrictive Legends. The shares issued in respect of your Award shall be endorsed with appropriate legends determined by the Company.

9. Award not a Service Contract.

(a) Your Continuous Service with the Company or an Affiliate is not for any specified term and may be terminated by you or by the Company or an Affiliate at any time, for any reason, with or without cause and with or without notice. Nothing in this Restricted Stock Unit Agreement (including, but not limited to, the vesting of your Award pursuant to the schedule set forth in Section 2 herein or the issuance of the shares in respect of your Award), the Plan or any covenant of good faith and fair dealing that may be found implicit in this Restricted Stock Unit Agreement or the Plan shall: (i) confer upon you any right to continue in the employ of, or affiliation with, the Company or an Affiliate; (ii) constitute any promise or commitment by the Company or an Affiliate regarding the fact or nature of future positions, future work assignments, future compensation or any other term or condition of employment or affiliation; (iii) confer any right or benefit under this Restricted Stock Unit Agreement or the Plan unless such right or benefit has specifically accrued under the terms of this Agreement or Plan; or (iv) deprive the Company of the right to terminate you at will and without regard to any future vesting opportunity that you may have.

(b) By accepting this Award, you acknowledge and agree that the right to continue vesting in the Award pursuant to the schedule set forth in Section 2 is earned only by continuing as an employee, director or consultant at the will of the Company (not through the act of being hired, being granted this Award or any other award or benefit) and that the Company has the right to reorganize, sell, spin-out or otherwise restructure one or more of its businesses or Affiliates at any time or from time to time, as it deems appropriate (a "reorganization"). You further acknowledge and agree that such a reorganization could result in the termination of your Continuous Service, or the termination of Affiliate status of your employer and the loss of benefits available to you under this Restricted Stock Unit Agreement, including but not limited to, the termination of the right to continue vesting in the Award. You further acknowledge and agree that this Restricted Stock Unit Agreement, the Plan, the transactions contemplated hereunder and the vesting schedule set forth herein or any covenant of good faith and fair dealing that may be found implicit in any of them do not constitute an express or implied promise of continued engagement as an employee or consultant for the term of this Agreement, for any period, or at all, and shall not interfere in any way with your right or the Company's right to terminate your Continuous Service at any time, with or without cause and with or without notice.

10. WITHHOLDING OBLIGATION.

(a) On or before the time you receive a distribution of the shares subject to your Award, or at any time thereafter as requested by the Company, you hereby authorize any required withholding (if any) from the Common Stock issuable to you and/or otherwise agree to make adequate provision in cash for any sums required to satisfy the federal, state, local and foreign tax withholding obligations (if any) of the Company or any Affiliate which arise in connection with your Award (the "***Withholding Obligation***"). Additionally, the Company may, in its sole discretion, satisfy all or any portion of the Withholding Obligation relating to your Award by any of the following means or by a combination of such means: (i) withholding from any compensation otherwise payable to you by the Company; (ii) causing you to tender a cash payment; or (iii) withholding shares of Common Stock from the shares of Common Stock issued or otherwise issuable to you in connection with the Award with a Fair Market Value (measured as of the date shares of Common Stock are issued to pursuant to Section 6) equal to the amount of such Withholding Obligation; provided, however, that the number of such shares of Common Stock so withheld shall not exceed the amount necessary to satisfy the Company's required tax withholding obligations using the minimum statutory withholding rates for federal, state, local and foreign tax purposes, including payroll taxes, that are applicable to supplemental taxable income.

(b) Unless the tax withholding obligations of the Company and/or any Affiliate are satisfied, the Company shall have no obligation to deliver to you any Common Stock.

(c) In the event the Company's obligation to withhold arises prior to the delivery to you of Common Stock or it is determined after the delivery of Common Stock to you that the amount of the Company's withholding obligation was greater than the amount withheld by the Company, you agree to indemnify and hold the Company harmless from any failure by the Company to withhold the proper amount.

(d) If specified in your Grant Notice and permitted by the Company, you may direct the Company to withhold shares of Common Stock with a Fair Market Value (measured as of the date shares of Common Stock are issued pursuant to Section 6) equal to the amount of such Withholding Obligation; provided, however, that the number of such shares of Common Stock so withheld shall not exceed the amount necessary to satisfy the Company's required tax withholding obligations using the minimum statutory withholding rates for federal, state, local and foreign tax purposes, including payroll taxes, that are applicable to supplemental taxable income.

11. UNSECURED OBLIGATION. Your Award is unfunded, and as a holder of a vested Award, you shall be considered an unsecured creditor of the Company with respect to the Company's obligation, if any, to issue shares pursuant to this Agreement. You shall not have voting or any other rights as a stockholder of the Company with respect to the shares to be issued pursuant to this Agreement until such shares are issued to you pursuant to Section 6 of this Agreement. Upon such issuance, you will obtain full voting and other rights as a stockholder of the Company. Nothing contained in this Agreement, and no action taken pursuant to its provisions, shall create or be construed to create a trust of any kind or a fiduciary relationship between you and the Company or any other person.

12. OTHER DOCUMENTS. You hereby acknowledge receipt or the right to receive a document providing the information required by Rule 428(b)(1) promulgated under the Securities Act, which includes the Plan prospectus. In addition, you acknowledge receipt of the Company's insider-trading policy and agree that you may sell shares only in compliance with such policy, in effect from time to time.

13. NOTICES. Any notices provided for in your Award or the Plan shall be given in writing and shall be deemed effectively given upon receipt or, in the case of notices delivered by the Company to you, five days after deposit in the United States mail, postage prepaid, addressed to you at the last address you provided to the Company. Notwithstanding the foregoing, the Company may, in its sole discretion, decide to deliver any documents related to participation in the Plan and this Award by electronic means or to request your consent to participate in the Plan by electronic means. You hereby consent to receive such documents by electronic delivery and, if requested, to agree to participate in the Plan through an on-line or electronic system established and maintained by the Company or another third party designated by the Company.

14. MISCELLANEOUS.

(a) The rights and obligations of the Company under your Award shall be transferable to any one or more persons or entities, and all covenants and agreements hereunder shall inure to the benefit of, and be enforceable by the Company's successors and assigns. Your rights and obligations under your Award may only be assigned with the prior written consent of the Company.

(b) You agree upon request to execute any further documents or instruments necessary or desirable in the sole determination of the Company to carry out the purposes or intent of your Award.

(c) You acknowledge and agree that you have reviewed your Award in its entirety, have had an opportunity to obtain the advice of counsel prior to executing and accepting your Award, and fully understand all provisions of your Award.

(d) This Agreement shall be subject to all applicable laws, rules, and regulations, and to such approvals by any governmental agencies or national securities exchanges as may be required.

(e) All obligations of the Company under the Plan and this Agreement shall be binding on any successor to the Company, whether the existence of such successor is the result of a direct or indirect purchase, merger, consolidation, or otherwise, of all or substantially all of the business and/or assets of the Company.

15. Governing Plan Document. Your Award is subject to all the provisions of the Plan, the provisions of which are hereby made a part of your Award, and is further subject to all interpretations, amendments, rules and regulations which may from time to time be promulgated and adopted pursuant to the Plan. Except as expressly provided herein, in the event of any conflict between the provisions of your Award and those of the Plan, the provisions of the Plan shall control.

16. Severability. If all or any part of this Agreement or the Plan is declared by any court or governmental authority to be unlawful or invalid, such unlawfulness or invalidity shall not invalidate any portion of this Agreement or the Plan not declared to be unlawful or invalid. Any Section of this Agreement (or part of such a Section) so declared to be unlawful or invalid shall, if possible, be construed in a manner which will give effect to the terms of such Section or part of a Section to the fullest extent possible while remaining lawful and valid.

17. Choice of Law. The interpretation, performance and enforcement of this Agreement will be governed by the law of the state of California without regard to such state's conflicts of laws rules.

18. Amendment. This Agreement may not be modified, amended or terminated except by an instrument in writing, signed by you and by a duly authorized representative of the Company. Notwithstanding the foregoing, this Agreement may be amended solely by the Board by a writing which specifically states that it is amending this Agreement, so long as a copy of such amendment is delivered to you, and provided that no such amendment adversely affecting your rights hereunder may be made without your written consent. Without limiting the foregoing, the Board reserves the right to change, by written notice to you, the provisions of this Agreement in any way it may deem necessary or advisable to carry out the purpose of the grant as a result of any change in applicable laws or regulations or any future law, regulation, ruling, or judicial decision, provided that any such change shall be applicable only to rights relating to that portion of the Award which is then subject to restrictions as provided herein.

19. Compliance with Section 409A of the Code. This Award is intended to comply with U.S. Treasury Regulation Section 1.409A-3(a) and will be construed and administered in such a manner. Each installment of Stock Units that vests hereunder is intended to constitute a "separate payment" for purposes of Treasury Regulation Section 1.409A-2(b)(2). If you are a Specified Employee upon your Separation from Service, then the issuance of any shares, cash or other property that would otherwise be made on the date of your Separation from Service (or within the first six months thereafter as a result of your Separation from Service) will not be made on the originally scheduled date(s) and will instead be issued in a lump-sum on the earlier of (i) the date that is six months and one day after the date of the Separation from Service, (ii) the date of your death or (iii) a 409A Change in Control, but if and only if such delay in the issuance is necessary to avoid the imposition of taxation on you in respect of the shares, cash or property under Code Section 409A.

*****

This Restricted Stock Unit Agreement shall be deemed to be signed by the Company and the Participant upon the signing by the Participant of the Restricted Stock Unit Grant Notice to which it is attached.

Exhibit 10.4

EXECUTION VERSION

Certain portions of this exhibit, marked by [***], have been excluded because they are both not material and are the type that the registrant treats as private or confidential

HTT RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT

AMONG

ISIS PHARMACEUTICALS, INC.,

AND

F. HOFFMANN-LA ROCHE LTD

AND

HOFFMANN-LA ROCHE INC.

HTT RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT

This HTT RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT (the "***Agreement***") is entered into as of the 8th day of April, 2013 (the "***Effective Date***") by and among **Isis Pharmaceuticals, Inc.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, California 92010 ("***Isis***"), and **F. Hoffmann-La Roche Ltd**, a Swiss corporation, having its principal place of business at Grenzacherstrasse 124, 4070 Basel, Switzerland ("***Roche Basel***") and **Hoffmann-La Roche Inc.**, a New Jersey corporation, having its principal place of business at 340 Kingsland Street, Nutley, New Jersey 07110 ("***Roche Nutley***"; Roche Basel and Roche Nutley are collectively referred to as "***Roche***"). Roche and Isis each may be referred to herein individually as a "***Party***" or collectively as the "***Parties***." Capitalized terms used in this Agreement, whether used in the singular or the plural, have the meaning set forth in Appendix 1. All attached appendices and schedules are a part of this Agreement.

RECITALS

WHEREAS, Isis has expertise in discovering and developing antisense drugs, and is researching compounds to identify and select a drug to treat Huntington's Disease;

WHEREAS, Roche has expertise in developing and commercializing drugs, and Roche is interested in researching, developing and commercializing an antisense drug to treat Huntington's Disease;

WHEREAS, Roche and Isis desire to conduct research activities to identify and select at least one antisense drug to treat Huntington's Disease;

WHEREAS, Roche and Isis also desire to conduct a research collaboration focused on discovering an antisense drug to treat Huntington's Disease using Roche's Brain Shuttle technology designed to deliver drugs through the blood-brain barrier;

WHEREAS, the Parties anticipate they will conduct the research programs in parallel with and without using Roche's Brain Shuttle technology, recognizing that Isis' non-Brain Shuttle program is further along in the research and development process, and that drugs from either or both program(s) may move forward in development based on emergent data and the commercial market of the individual drugs; and

WHEREAS, Roche desires Isis to develop the HTT drug through completion of the initial Phase 1 Trial and grant Roche an option to obtain an exclusive license to develop and commercialize such drug;

NOW, THEREFORE, in consideration of the respective covenants, representations, warranties and agreements set forth herein, the Parties hereto agree as follows:

ARTICLE 1.
RESEARCH AND DEVELOPMENT

1.1. **Overview**. The intent of the Collaboration is for the Parties to conduct two research programs in parallel focused on (i) an Isis HTT program initially centered around the research of Allele Selective Compounds and Non-Allele Selective Compounds to designate an Isis Development Candidate, and (ii) a collaborative HTT program between Isis and Roche, funded by Roche, involving Roche's proprietary technology designed to enhance delivery of molecules through the blood-brain barrier ("***Brain Shuttle***"), where the Parties will combine an Isis Compound with such Brain Shuttle technology to develop a Brain Shuttle Development Candidate. From the Effective Date until the date the Option is exercised, expires or is terminated (the "***Option Period***"), Isis will Develop and fund the initial Isis Development Candidate through the first Phase 1 Trial, and Roche will have an Option to obtain an exclusive license to further Develop and Commercialize the Development Candidates. Drugs from either or both program(s) may move forward in development based on data and the commercial market of the individual drugs. If Roche exercises its Option, Roche will be responsible for all further pre-clinical, clinical, regulatory, manufacturing and commercial activities related to Products. The purpose of this Section 1.1 is to provide a high-level overview of the roles, responsibilities, rights and obligations of each Party under this Agreement with regard to the R&D Plans and Products, and therefore this Section 1.1 is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

1.2. **Isis Development Candidate-R&D Plan**.

1.2.1. **Isis Development Candidate-R&D Plan Activities**. The Isis Development Candidate-R&D Plan is attached hereto as Appendix 2, and sets forth the research and development activities the Parties will conduct during the Option Period with the first Compound designated an Isis Development Candidate, and through completion of the Registration-Directed Trials. As of the Effective Date, the Isis Development Candidate-R&D Plan focuses primarily on the research and Development of Non-Allele Selective Compounds, and is intended to achieve designation of one Isis Development Candidate and one Back-Up Compound. If the Parties subsequently decide to expand the efforts under such plan on the research and Development of Allele Selective Compounds, the Parties will mutually agree on any appropriate changes to the Isis Development Candidate-R&D Plan, with Roche being responsible for the incremental cost of any such changes.

1.2.2. **Conducting the Isis Development Candidate-R&D Plan**. During the Option Period, Roche and Isis will each use Commercially Reasonable Efforts to conduct the research and Development activities designated for each of them, respectively under the Isis Development Candidate-R&D Plan in accordance with the timelines specified therein, giving due consideration to the recommendations and advice of the JSC; *provided*, neither Roche nor Isis will have any obligation to perform any activity that, after having consulted the JSC, it in good faith believes that continuing such activity would violate any Applicable Law, ethical principles, or principles of scientific integrity.

1.2.3. **Isis' Performance Milestones**. During the Option Period, Isis will use Commercially Reasonable Efforts to:

(a) Designate at least one Isis Development Candidate by [***]; *provided, however*, that if research or Development issues arise that are outside of Isis' reasonable control and make such designation by such date impossible, the Parties will negotiate in good faith to revise the date by which Isis may designate an Isis Development Candidate;

(b) Within [***] designating an Isis Development Candidate, complete the [***] for such Isis Development Candidate; and

(c) Within [***] are completed for an Isis Development Candidate and Isis has obtained the [***], [***], [***] and [***] data generated from such [***] sufficient to support the [***], [***] for such Isis Development Candidate.

1.2.4. **Notice of Isis Development Candidate Designation**. When Isis first designates an Isis Development Candidate, Isis will notify Roche in writing promptly after such designation and, together with such notice, will provide Roche the applicable Development Candidate Data Package.

1.2.5. **Isis Development Candidate IND-Enabling Toxicology Studies**. Once available to Isis, Isis will promptly deliver to Roche the pharmacology, toxicology, histology and pharmacokinetic data generated from the IND-Enabling Toxicology Studies under the Isis Development Candidate-R&D Plan.

1.2.6. **Phase 1 Trial**. Isis will keep the JSC informed of the progress of the Phase 1 Trial. Once available to Isis, Isis will promptly deliver to Roche the applicable Phase 1 Trial Data Package.

1.2.7. [***]. Prior to the Initiation of the [***] for the Isis Development Candidate, the Parties will discuss and mutually agree on whether to conduct an [***] for such Isis Development Candidate. If the Parties mutually agree to conduct such an [***], then the [***] will be considered an Approved Change to the Isis Development Candidate-R&D Plan and the costs to conduct such [***] will be treated as Additional Costs in accordance with Section 1.6.1(b).

1.3. **Conducting the Brain Shuttle Development Candidate-R&D Plan**. In addition to the Isis Development Candidate-R&D Plan performed under Section 1.2 above, Roche and Isis will conduct a research collaboration under the Brain Shuttle Development Candidate-R&D Plan to identify a Brain Shuttle Development Candidate. The Brain Shuttle Development Candidate-R&D Plan is attached hereto as Appendix 3 and sets forth the research activities the Parties will conduct through designation of the Brain Shuttle Development Candidate. Once the first Brain Shuttle Development Candidate is designated, Roche will update the Brain Shuttle Development Candidate-R&D Plan to cover Development activities for the first Brain Shuttle Development Candidate through the completion of Registration-Directed Trials, which plan will be consistent with the level of effort and diligence set forth in the Isis Development Candidate-R&D Plan. Changes to the Brain Shuttle Development Candidate-R&D Plan that affect the Isis R&D Activities thereunder must be unanimously agreed to by the JSC or, if the JSC no longer exists, by the Parties. Roche and Isis will each use Commercially Reasonable Efforts to conduct the research and Development activities designated for each of them, respectively under the Brain Shuttle Development Candidate-R&D Plan in accordance with the timelines specified therein, giving due consideration to the recommendations and advice of the JSC; *provided*, neither Roche nor Isis will have any obligation to perform any activity that, after having consulted the JSC, it in good faith believes that continuing such activity would violate any Applicable Law, ethical principles, or principles of scientific integrity.

1.3.1. **Brain Shuttle Development Candidate Designation**. If Roche, after consultation with the JSC, determines a Compound under the Brain Shuttle Development Candidate-R&D Plan is ready to start IND-Enabling Toxicology Studies, such Compound will be a "***Brain Shuttle Development Candidate***."

1.3.2. **Brain Shuttle Development Candidate IND-Enabling Toxicology Studies**. Once available to Roche, Roche will promptly deliver to Isis the pharmacology, toxicology, histology and pharmacokinetic data generated from the IND-Enabling Toxicology Studies under the Brain Shuttle Development Candidate-R&D Plan.

1.3.3. **Phase 1 Trial**. Roche will use Commercially Reasonable Efforts to conduct the Phase 1 Trial for the Brain Shuttle Development Candidate under the Brain Shuttle Development Candidate-R&D Plan. Roche will keep Isis informed of the progress of each Phase 1 Trial through the JSC.

1.4. **Disclosure of Results**. Each Party will promptly disclose to the other Party via disclosure at JSC meetings the results of work performed by such Party under each R&D Plan. Isis and Roche will provide reports and analyses at each JSC meeting, and more frequently on reasonable request by the JSC, detailing the current status of each R&D Plan. If the JSC has dissolved, then each Party will promptly disclose such data and results directly to the other Party.

1.5. Development Management.

1.5.1. **JSC**. The Parties will establish a joint steering committee (the "***JSC***") to provide advice and make recommendations on the conduct of the Collaboration consistent with the R&D Plans. The JSC will act as a forum for sharing information about the activities conducted by the Parties hereunder, as an advisory body, and will have decision-making authority to the extent set forth on SCHEDULE 1.5.1. The JSC will consist of two (2) qualified representatives appointed by Isis, and two (2) qualified representatives appointed by Roche. Prior to Option exercise, Isis will designate one of its representatives to act as the chairperson of the JSC. After Option exercise, Roche will designate one of its representatives to act as the chairperson of the JSC. The chairperson will be responsible for overseeing the activities of the JSC. SCHEDULE 1.5.1 sets forth certain JSC governance matters. The JSC will determine the JSC operating procedures at its first meeting, which will be codified in the written minutes of the first JSC meeting. In addition, during the term of the JSC, CHDI will have the right to participate in JSC meetings as a non-voting observer; *provided*, *however*, if Isis and Roche reasonably determine in good faith after discussion with CHDI that, due to participation in programs with a potentially competitive drug, CHDI should no longer participate in JSC meetings and be exposed to program data, then Isis will provide CHDI with written notice of such determination and thereafter CHDI will no longer participate in meetings of the JSC. The CHDI observer shall be a person reasonably acceptable to both Roche and Isis.

1.5.2. **Decision Making**.

(a) ***Under the Isis Development Candidate-R&D Plan***. Prior to Option exercise, except as provided below in Section 1.5.2(b), Isis will have the final decision-making authority regarding the conduct of the Isis Development Candidate-R&D Plan, and whether to accept and how to implement the JSC's recommendations.

(b) ***With Respect to All Subsequent Isis Development Candidates***. For the second and any subsequent Isis Development Candidates, subject to Section 1.5.2(e), Roche will have the final decision-making authority regarding whether to Initiate the IND-Enabling Toxicology Studies and all subsequent Development activities thereafter. If the first Compound designated an Isis Development Candidate is no longer being Developed, then the next Compound designated an Isis Development Candidate that takes its place will still be considered the "first" Isis Development Candidate for purposes of this Section 1.5.2(b), and the Isis Development Candidate-R&D Plan will be amended accordingly as mutually agreed by the Parties to cover any research and Development activities and related costs for such replacement Isis Development Candidate in accordance with Section 1.8 below.

(c) ***Under the Brain Shuttle Development Candidate-R&D Plan***. Subject to Section 5.1 and Section 1.5.2(e), Roche will have the final decision-making authority regarding selection of Brain Shuttle Development Candidates, the conduct of the Brain Shuttle Development Candidate-R&D Plan, and whether to accept and how to implement the JSC's recommendations.

(d) ***Development Decision Making After Option Exercise***. After Option exercise and without limiting Roche's obligations under this Agreement to use Commercially Reasonable Efforts, Roche will have the final decision making authority for which Products to Initiate Phase 2 and all subsequent Clinical Trials. In addition, Roche will have full responsibility for designing, conducting, funding and implementing the further Development of Products, including clinical trials and regulatory submissions.

(e) ***Exceptions***. If Roche's exercise of its decision-making authority pursuant to Section 1.5.2(b), Section 1.5.2(c) or Section 1.5.2(d) would increase costs for any Isis R&D Activities, then such decision must be unanimously agreed to by the JSC or, if the JSC no longer exists, by the Parties.

1.5.3. **Alliance Managers**. Each Party will appoint a representative to act as its alliance manager (each, an "***Alliance Manager***"). Each Alliance Manager will be responsible for supporting the JSC and performing the activities listed in SCHEDULE 1.5.3.

1.6. **Collaboration Costs and Expenses**.

1.6.1. **Isis Development Candidate-R&D Plan**.

(a) **Isis Development Candidate-R&D Plan Costs – Generally**. During the Option Period, except as otherwise provided under Section 1.6.1(b), Isis will be responsible for all costs and expenses associated with the Isis R&D Activities designated under the Isis Development Candidate-R&D Plan for the first Compound designated an Isis Development Candidate, and Roche will be responsible for all costs and expenses associated with any Roche R&D Activities designated under the Isis Development Candidate-R&D Plan. Isis cannot change any of the Roche R&D Activities without the unanimous agreement of the JSC or, if the JSC no longer exists, Roche. As provided in Section 1.8, Roche is responsible for the costs of any research and Development activities for an Additional Isis Development Candidate.

(b) **Additional Costs Associated with Approved Changes to the Isis Development Candidate-R&D Plan**. Roche will be responsible for paying Isis quarterly in advance for any Additional Costs resulting from Approved Changes. Roche will review and approve the Additional Costs before any Approved Changes are implemented by Isis. Isis and Roche will update the Isis Development Candidate-R&D Plan to reflect any such Approved Changes and Isis will invoice Roche for any such Additional Costs quarterly in advance after such Additional Costs are approved. Isis may reasonably estimate its FTE time required to perform the Approved Changes. Roche will pay the invoices submitted pursuant to this Section 1.6.1(b) for such approved Additional Costs within thirty (30) days after Roche's receipt of the applicable invoice. Isis will use its Commercially Reasonable Efforts to complete Approved Changes within the amount of the agreed Additional Costs. If at any time during the performance of the Approved Changes, Isis expects its actual Additional Costs to be greater than [***] of the previously agreed Additional Costs for a particular Approved Change(s) (the difference being "***Change Overruns***"), then Isis shall promptly notify the JSC which will then discuss and agree whether the Approved Changes should continue, and if so, how the Parties shall share the cost of any Change Overruns. Any Change Overruns Roche agrees to pay will be considered Additional Costs. Unless approved by Roche, Roche will not be responsible for Change Overruns that are greater than [***] of the previously agreed Additional Costs for a particular Approved Change(s).

(c) **Reconciliation of Any Overpayment or Underpayment of Additional Costs**. At the end of every second (2nd) and fourth (4th) Calendar Quarter during any period where Additional Costs are incurred (and again at the completion of all of the Approved Changes), Isis will provide Roche with an accounting of actual costs incurred by Isis (including Isis' estimated FTE costs) compared to the Additional Costs paid in advance by Roche. After such accounting, if Isis' actual costs incurred were greater than the Additional Costs paid in advance by Roche, then Roche will pay Isis the amount of such difference within thirty (30) days after Isis provides the accounting to Roche and Roche's receipt of an invoice from Isis. If, however, after such accounting Isis' actual costs incurred were less than the Additional Costs paid in advance by Roche, then Isis will provide Roche the amount of such difference in the form of a credit against the next payment (including any future payments for any then ongoing Approved Changes) to be paid by Roche to Isis under this Agreement.

1.6.2. **Brain Shuttle Development Candidate-R&D Plan**.

(a) **Brain Shuttle Development Candidate-R&D Plan Costs**. Roche will be responsible for all costs and expenses associated with the Brain Shuttle Development Candidate-R&D Plan, including pre-clinical *in vitro* or *in vivo* efficacy studies costs, manufacturing costs, IND-Enabling Toxicology Study costs, chronic toxicology study costs, clinical trial costs (including OLE Trial costs), and all costs and expenses associated with the Isis R&D Activities and the Roche R&D Activities designated under the Brain Shuttle Development Candidate-R&D Plan.

(b) **Brain Shuttle Development Candidate-R&D Plan – Cost Estimates and Invoicing**.

(i) ***Brain Shuttle Program Cost Estimate***. Roche will pay Isis in advance on a quarterly basis for Isis' performance of the Isis R&D Activities designated under the Brain Shuttle Development Candidate-R&D Plan to progress to the next significant stage of research or development at the then-applicable Isis FTE Rate, plus any reasonable out-of-pocket expenses incurred by Isis in performing such work. The costs of ASOs to be supplied by Isis under the Brain Shuttle Development Candidate-R&D Plan will be calculated in accordance with SCHEDULE 1.6.2(b)(i). Isis may reasonably estimate its FTE time required to perform the Isis R&D Activities designated under the Brain Shuttle Development Candidate-R&D Plan. Each time the Parties agree to, or expand, the Isis R&D Activities under the Brain Shuttle Development Candidate-R&D Plan, Isis will provide Roche with a good faith estimate of the internal and external costs (each such estimate, a "***Brain Shuttle Program Cost Estimate***") to conduct such Isis R&D Activities to the end of the next significant stage of research or development, and Isis and Roche will endeavor to mutually agree on a final Brain Shuttle Program Cost Estimate.

(ii) ***Payment Schedule and Invoicing; Reconciliation of Any Overpayment or Underpayment of Additional Costs***. Once a given Brain Shuttle Program Cost Estimate is finalized under Section 1.6.2(b)(i) and Isis is ready to start such work, Isis will deliver to Roche each quarter in advance an invoice for Isis' estimated costs for the coming Calendar Quarter. Roche will pay Isis within thirty (30) days after receiving such invoice. Isis will use its Commercially Reasonable Efforts to complete the Isis R&D Activities related to a given Brain Shuttle Program Cost Estimate within the amount of the agreed Brain Shuttle Program Cost Estimate. For each Brain Shuttle Program Cost Estimate, Isis and Roche will handle any cost overruns and reconciliations of any overpayment or underpayment of Additional Costs using the same process used under Section 1.6.1(b) and Section 1.6.1(c) above.

1.7. **Manufacturing and Supply**.

1.7.1. **Isis Development Candidate-R&D Plan**.

(a) **Supplies for Activities During the Option Period**. During the Option Period, [***], for the first Compound designated an Isis Development Candidate, Isis will supply API, finished Product and any research-grade Compound sufficient to support the Isis R&D Activities designated under the Isis Development Candidate-R&D Plan. In addition, during the Option Period, for the first Compound designated an Isis Development Candidate, Isis will supply API, finished Product, and research-grade Compound sufficient to support any Roche R&D Activities designated under the Isis Development Candidate-R&D Plan, and Isis will provide Roche with such API and finished Product [***].

(b) **Supplies for Activities After Option Exercise**. After Option exercise, Isis will deliver to Roche, if Roche desires, any inventory of cGMP API, non-GMP API, radiolabeled material, GMP and non-GMP finished Product, packaged clinical trial material, and non-GMP packaged trial material containing the Isis Development Candidate in Isis' possession [***].

1.7.2. **Supplies for Activities under the Brain Shuttle Development Candidate-R&D Plan**. The Parties will mutually agree on the quantity of API and research-grade Compound needed to support the Isis R&D Activities and Roche R&D Activities designated under the Brain Shuttle Development Candidate-R&D Plan. Roche will be responsible for all costs and expenses associated with supply of research-grade Compound, API and finished Product under the Brain Shuttle Development Candidate-R&D Plan.

1.8. **Requests to Work on an Additional Isis Development Candidate**.

1.8.1. ***Requests During the Option Period***.

(a) If, during the Option Period, Roche provides Isis a written request to discover and Develop a replacement or second Isis Development Candidate ("***Additional Isis Development Candidate***"), Isis will use Commercially Reasonable Efforts to perform such work under a mutually agreed amendment to the Isis Development Candidate-R&D Plan. The cost to perform such work leading up to the IND-Enabling Toxicology Studies will be paid by Roche in accordance with Section 1.8.3 below.

(b) If, during the Option Period, Roche provides Isis a written request to perform the IND-Enabling Toxicology Studies for the Additional Isis Development Candidate, Isis will use Commercially Reasonable Efforts to perform such work under a mutually agreed amendment to the Isis Development Candidate-R&D Plan. If the first Compound designated an Isis Development Candidate is being Developed under this Agreement when Isis receives such written request from Roche, then in lieu of Isis' actual costs to conduct the IND-Enabling Toxicology Studies on such Additional Isis Development Candidate, Roche shall pay Isis [***]. If, however, the first Compound designated an Isis Development Candidate has already completed IND-Enabling Toxicology Studies but is no longer being Developed under this Agreement when Isis receives such written request from Roche, then the [***] shall NOT be paid by Roche. Instead, Isis' [***] to conduct the IND-Enabling Toxicology Studies for the Additional Isis Development Candidate will be paid by Roche in accordance with Section 1.8.3 below.

1.8.2. ***Requests After Option Exercise***. If, after Option exercise, Roche provides Isis a written request to discover an Additional Isis Development Candidate, then Isis will use Commercially Reasonable Efforts to discover an Additional Isis Development Candidate under a mutually agreed amendment to the Isis Development Candidate-R&D Plan, and once such Additional Isis Development Candidate is designated, Roche will be responsible for conducting the IND-Enabling Toxicology Studies for such Additional Isis Development Candidate. The cost to perform the work to discover an Additional Isis Development Candidate will be paid by Roche in accordance with Section 1.8.3 below. Roche's right to request Isis to perform the work described in this Section 1.8.2 expires [***], or if [***] but in no case later than [***] days after the [***].

1.8.3. ***Additional Isis Development Candidate-Cost Estimate - Payment Mechanics***. Before Isis starts any work requested under Section 1.8.1(a), Section 1.8.1(b) (if applicable), or Section 1.8.2, the Parties will finalize (via the JSC) a mutually agreed cost estimate covering Isis' estimate of its [***] by Isis in performing such work (including the cost of API and finished Product) (the "***Additional Isis Development Candidate-Cost Estimate***"). Before Isis commences any such work, Isis will provide the JSC with a good faith estimate of the cost for Isis to conduct and complete such work, and the JSC will discuss and unanimously agree on a final Additional Isis Development Candidate-Cost Estimate for Isis to conduct such activities. Isis will invoice Roche and Roche will pay Isis the Additional Isis Development Candidate-Cost Estimate using the same payment mechanism and schedule used under Section 1.6.1(b) and Section 1.6.1(c) above for Additional Costs.

1.9. **Subcontracting**. Each Party may engage Third Party subcontractors to perform certain of its obligations under this Agreement. Any subcontractor engaged to perform a Party's obligations under this Agreement will meet the qualifications typically required by such Party for the performance of work similar in scope and complexity and will execute such Party's standard nondisclosure agreement. Any Party engaging a subcontractor hereunder will remain responsible for such activities.

1.10. **Materials Transfer**. To facilitate the activities under an R&D Plan, either Party may provide certain materials for use by the other Party. All such materials will be used by the receiving Party in accordance with terms of this Agreement solely for purposes of exercising its rights and performing its obligations under this Agreement, and the receiving Party will not transfer such materials to any Third Party except with the written consent of the supplying Party. Except as expressly set forth herein, THE MATERIALS ARE PROVIDED "AS IS" AND WITHOUT ANY REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR OF FITNESS FOR ANY PARTICULAR PURPOSE OR ANY WARRANTY THAT THE USE OF THE MATERIALS WILL NOT INFRINGE OR VIOLATE ANY PATENT OR OTHER PROPRIETARY RIGHTS OF ANY THIRD PARTY.

1.11. **Applicable Laws**. Each Party will perform its activities pursuant to this Agreement in compliance with good laboratory and clinical practices and cGMP, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted.

1.12. **Failure to Designate an Isis Development Candidate**. If, despite Isis' Commercially Reasonable Efforts, by the [***] anniversary of the Effective Date, Isis has not designated an Isis Development Candidate, then, notwithstanding any provision to the contrary in this Agreement (i) work under the Isis Development Candidate-R&D Plan will stop; (ii) the Parties' will no longer have an obligation to perform any activities under this ARTICLE 1 with respect to the Isis Development Candidate-R&D Plan; (iii) the Parties' respective obligations and Roche's rights under this Agreement with respect to the Isis Development Candidate-R&D Plan and any related Compounds will then terminate; (iv) Isis will have exclusive rights (and Roche will, and hereby does grant Isis an exclusive license) to all data, results and information generated under the Isis Development Candidate-R&D Plan, and Roche will promptly transfer to Isis copies of all such data, results and information in Roche's possession; and (v) Roche will and hereby does grant Isis an irrevocable, royalty-free, non-exclusive license to any Know-How and/or Patent Rights generated by Roche under the Isis Development Candidate-R&D Plan to research, develop, manufacture and commercialize ASOs designed to bind to the RNA encoding HTT. Isis will control any Jointly-Owned Collaboration Patents that resulted from the Isis Development Candidate-R&D Plan, and Roche will assign ownership to Isis on condition that Isis grants Roche an irrevocable, royalty-free, non-exclusive license for any purpose (other than researching, developing, manufacturing or commercializing products comprising an ASO).

1.13. **Failure to Designate a Brain Shuttle Development Candidate**. If, despite the Parties' Commercially Reasonable Efforts, by the [***] anniversary of the Effective Date, Roche has not designated a Brain Shuttle Development Candidate, then, notwithstanding any provision to the contrary in this Agreement (i) work under the Brain Shuttle Development Candidate-R&D Plan will stop; (ii) the Parties' will no longer have an obligation to perform any activities under this ARTICLE 1 with respect to the Brain Shuttle Development Candidate-R&D Plan; and (iii) the Parties' respective obligations and Roche's rights under this Agreement with respect to the Brain Shuttle Development Candidate-R&D Plan and any related Compounds will then terminate.

ARTICLE 2.
EXCLUSIVITY COVENANTS

2.1. **Exclusivity**.

2.1.1. **Exclusivity Covenants**. Each Party agrees that, except in the performance of its obligations or exercise of its rights under this Agreement, and except as set forth in Section 2.1.2 or Section 2.1.3:

(a) **The Parties' Exclusivity Covenants During the Option Period**. During the Option Period, each Party will work exclusively within the collaboration described in the Agreement to conduct all discovery, research, development, manufacture or commercialization of an ASO that is designed to bind to the RNA that encodes HTT in the Field.

(b) **The Parties' Exclusivity Covenants After Option Exercise**. After Option exercise:

(i) ***Developing an NAS Development Candidate***. If Roche is Developing or Commercializing a Development Candidate comprising a Non-Allele Selective Compound (an "***NAS Development Candidate***"), then until the Full Royalty Period ends in the first Major Market, neither Party nor any of its Affiliates or Sublicensees will sell an ASO approved by a Regulatory Authority for marketing and sale that is designed to bind to the RNA that encodes HTT in the Field. After the end of the Full Royalty Period in the first Major Market, the exclusivity covenants will continue on a country-by-country basis in each country where the Full Royalty Period still applies [***].

If, during the Reduced Royalty Period for such NAS Development Candidate, Isis (on its own or with a Third Party) following marketing approval sells an ASO designed to bind to the RNA that encodes HTT in the Field, then [***] and Roche's worldwide license under Section 4.1.1 solely with respect to such NAS Development Candidate will [***]; or

(ii) ***Developing an AS Development Candidate***. If (and for as long as) Roche is Developing or Commercializing a Development Candidate comprising an Allele Selective Compound (an "***AS Development Candidate***"), then through [***] prior to the anticipated end of the Full Royalty Period in the relevant country, neither Party nor any of its Affiliates or Sublicensees will file an NDA, MAA or JNDA, as applicable, for an ASO that is designed to bind to an SNP site within an HTT RNA associated with an expanded CAG repeat to selectively reduce the expanded CAG-repeat containing RNA relative to the normal HTT RNA (each such ASO, an "***AS ASO***"); *provided*, *however*, that if within [***] for such AS Development Candidate but in no case later than [***], Roche does not request Isis to research and develop a second AS Development Candidate designed for use in a patient population substantially different from the patient population for the AS Development Candidate being developed or commercialized by Roche (as determined by genetic testing) (or if Roche later stops Developing or Commercializing such AS ASO), then, subject to the potential [***], Isis, its Affiliates or Sublicensees may sell AS ASOs designed for use in a patient population substantially different from the patient population for the AS Development Candidate being developed or commercialized by Roche (as determined by [***]) where [***] (Y) [***], or (Z) [***].

2.1.2. **Limitations and Exceptions to Isis' Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, Isis' practice of the following will not violate Section 2.1.1:

(a) Performance of the Isis R&D Activities;

(b) Any activities pursuant to the Prior Agreements as in effect on the Effective Date; and

(c) The granting of, or performance of obligations or exercise of rights under, Permitted Licenses.

2.1.3. **Limitations and Exceptions to Roche's Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, Roche's performance of the Roche R&D Activities will not violate Section 2.1.1.

2.2. **Effect of Exclusivity on Indications**. Isis and Roche are subject to certain exclusivity covenants under Section 2.1; *however*, the Parties acknowledge and agree that each Party (on its own or with a Third Party) may pursue products for any indication that are not designed to bind to the RNA that encodes HTT (or designed to selectively reduce HTT RNA alleles containing expanded CAG repeats), even if such products treat Huntington's Disease.

ARTICLE 3.
EXCLUSIVE OPTION

3.1. **Option and Option Deadline**. Isis hereby grants Roche an exclusive option to obtain the license set forth in Section 4.1.1 (the "***Option***"). To obtain the license set forth in Section 4.1.1, Roche must exercise the Option by the earlier of the following (the "***Option Deadline***"): (i) the [***] following Roche's receipt of the Phase 1 Trial Data Package from Isis under Section 1.2.6 for the first Phase 1 Trial with an Isis Development Candidate (as such Phase 1 Trial is described in the Isis Development Candidate R&D Plan or as may otherwise be modified by the JSC); or (ii) [***] the Phase 1 Trial Data Package is available in the first Phase 1 Trial for a Brain Shuttle Development Candidate but in no case later than [***] after the last patient receives his/her last dose in such Phase 1 Trial; or (iii) [***].

3.2. **Option Exercise; Option Expiration**. If, by the Option Deadline, Roche (i) notifies Isis in writing that it is exercising the Option, and (ii) thereafter, Roche timely pays Isis the license fee set forth in Section 6.3, Isis will, and hereby does, grant Roche the license set forth in Section 4.1.1. Prior to the Option Deadline, Roche shall have the full opportunity to conduct due diligence to evaluate whether to exercise the Option and Isis shall cooperate with Roche and to ensure that all necessary data and information, including clinical and manufacturing data and any available [***] analysis, are provided to Roche. If, by the Option Deadline, Roche has not provided Isis a written notice stating that Roche is exercising its Option, and within thirty (30) days after providing such notice paid Isis the license fee set forth in Section 6.3, then Roche's Option will expire. If Roche's Option expires then Section 10.4.1 and Section 10.4.2 will apply.

3.3. **HSR**. If, by the Option Deadline, Roche notifies Isis in writing that it is exercising the Option, each Party shall (i) cooperate with the other Party in the preparation, execution and filing of all documents that may be required pursuant to the HSR Act or any other Applicable Law, and (ii) observe all applicable waiting periods before consummating the Option Exercise as set forth in Section 3.2. Each Party shall bear its own costs (including counsel or other expert fees) with respect to preparing, executing and filing such documents. Subject to the terms and conditions of this Agreement, each Party shall use all reasonable efforts to take, or cause to be taken, all reasonable actions and to do, or cause to be done, all things necessary and appropriate to consummate the exercise of the Option contemplated by Section 3.2 of this Agreement, should Roche choose to exercise the Option. Notwithstanding anything to the contrary contained in this Agreement, Roche shall have the sole and exclusive right to determine, at its discretion but without any obligation whatsoever, whether it shall have any obligation to take any actions in connection with, or agree to, any demands for the license, sale, divestiture or disposition of assets of Roche or its Affiliates or Isis, asserted by the United States Federal Trade Commission, the Antitrust Division of the United States Department of Justice or any other Regulatory Authority in connection with antitrust matters or international competition laws, or to defend through litigation any proceeding commenced by the Federal Trade Commission, the Antitrust Division of the United States Department of Justice or other Governmental Authority in connection with the foregoing matters.

ARTICLE 4.
LICENSE GRANTS

4.1. **License Grants; Sublicense Rights**.

4.1.1. **Development and Commercialization License Grant to Roche**. Subject to the terms of this Agreement, effective upon Roche's exercise of the Option in accordance with this Agreement, Isis grants to Roche a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.4 below) license under the Licensed Technology to research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.4 below) and Commercialize Products in the Field.

4.1.2. **Brain Shuttle IP Licenses**. As further specified in Section 7.1.3, the Joint Patent Committee will classify the Brain Shuttle Collaboration Patents into the following sub-categories: (w) Brain Shuttle-Specific Collaboration Patents, (x) ASO-Specific Collaboration Patents, (y) Linker-Specific Collaboration Patents, and (z) Omnibus Collaboration Patents. With respect to each such sub-category of Brain Shuttle Collaboration Patents, the Parties grant one another the following licenses:

(a) ***Licenses to Roche to Brain Shuttle Collaboration Patents***. Subject to the terms of this Agreement, Isis hereby grants to Roche:

(i) a worldwide, exclusive, sublicensable license under any Brain Shuttle-Specific Collaboration Patents, Linker-Specific Collaboration Patents and Omnibus Collaboration Patents solely or jointly-owned by Isis or its Affiliates, to research, develop, manufacture, have manufactured and commercialize products comprising an active pharmaceutical ingredient and the Brain Shuttle Technology (each such product, a "***BS-Specific Drug***"); and

(ii) a worldwide, non-exclusive, sublicensable license under any Linker-Specific Collaboration Patents and Omnibus Collaboration Patents solely or jointly-owned by Isis or its Affiliates, to research, develop, manufacture, have manufactured and commercialize products.

(b) ***Licenses to Isis to Brain Shuttle Collaboration Patents***. Subject to the terms of this Agreement (including Isis' exclusivity covenants under Section 2.1.1), Roche hereby grants to Isis:

(i) a worldwide, exclusive, sublicensable license under any ASO-Specific Collaboration Patents, Linker-Specific Collaboration Patents and Omnibus Collaboration Patents solely or jointly-owned by Roche or its Affiliates, to research, develop, manufacture, have manufactured and commercialize products that include an ASO as an active pharmaceutical ingredient and are not BS-Specific Drugs; and

(ii) a worldwide, non-exclusive, sublicensable license under any Linker-Specific Collaboration Patents and Omnibus Collaboration Patents solely or jointly-owned by Roche or its Affiliates, to research, develop, manufacture, have manufactured and commercialize products.

4.1.3. **Amendment to the Existing Diagnostic Agreement**. After Option exercise, Isis and Roche will execute an amendment to the Existing Diagnostic Agreement on terms mutually agreed by Roche and Isis, which amendment will include granting Roche a non-exclusive, sublicensable, worldwide license, with the right to sublicense (through multiple tiers) under Patent Rights and/or Know-How Controlled by Isis necessary or useful to develop and commercialize HTT diagnostic products (including diagnostic products and/or services to select patients who will use Products).

4.1.4. **Sublicense Rights**.

(a) Subject to the terms of this Agreement, Roche will have the right to grant sublicenses under any license granted under Section 4.1.1 above:

(i) under the Isis Core Technology Patents, Isis Product-Specific Patents and Isis Know-How to an Affiliate of Roche or a Third Party; and

(ii) under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How solely to (y) an Affiliate of Roche or (z) [***] (each, a "***Licensed CMO***").

(b) **Requests to Grant Sublicenses to CMOs**. If Roche provides Isis with a written request that Isis grant a license under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How to a CMO designated by Roche that is not a Licensed CMO, solely for such CMO to manufacture Products for Roche, its Affiliate or Sublicensee in a manufacturing facility owned or operated by such CMO, [***].

(c) **Enforcing Sublicenses**. Each sublicense by Roche under this Agreement will be subject to, and consistent with, the terms of this Agreement. Roche shall be responsible to ensure compliance by its Sublicensees with the terms and conditions of this Agreement. If Isis reasonably believes a Roche Sublicensee may be violating the terms of this Agreement, then, within 30 days after Isis delivers a written request to Roche, Roche will provide Isis a full and complete copy of the sublicense Roche entered with such Sublicensee.

(d) **Effect of Termination on Sublicenses**. If this Agreement terminates for any reason, any Sublicensee granted a sublicense by Roche to Develop or Commercialize Products will, from the effective date of such termination, automatically become a direct licensee of Isis with respect to the rights sublicensed to the Sublicensee by Roche; *so long as* (i) such Sublicensee is not in breach of its sublicense agreement, (ii) such Sublicensee agrees in writing to comply with all of the terms of this Agreement to the extent applicable to the rights originally sublicensed to it by Roche, and (iii) such Sublicensee agrees to pay directly to Isis such Sublicensee's payments under this Agreement to the extent applicable to the rights sublicensed to it by Roche. Roche agrees that it will confirm clause (i) of the foregoing in writing at the request and for the benefit of Isis and if requested, the Sublicensee.

4.1.5. **No Implied Licenses**. All rights in and to Licensed Technology not expressly licensed to Roche under this Agreement are hereby retained by Isis or its Affiliates. All rights in and to Roche Technology not expressly licensed or assigned to Isis under this Agreement, are hereby retained by Roche or its Affiliates. Except as expressly provided in this Agreement, no Party will be deemed by estoppel or implication to have granted the other Party any license or other right with respect to any intellectual property.

4.1.6. **License Conditions; Limitations**. Subject to Section 6.11, any license granted under Section 4.1.1 and the sublicense rights under Section 4.1.4 are subject to and limited by (i) the Permitted Licenses, (ii) the Prior Agreements, and (iii) the Isis In-License Agreements, in each case to the extent the provisions of such obligations or agreements are specifically disclosed to Roche in writing (or via electronic data room).

4.1.7. **Trademarks for Products**. After Option exercise, Roche is solely responsible for all trademarks, trade dress, logos, slogans, designs, copyrights and domain names used on or in connection with Products licensed under Section 4.1.1.

4.2. **Technology Transfer after Option Exercise**. After Option exercise pursuant to a technology transfer plan to be mutually agreed by Isis and Roche, and subject to Section 4.2.3, Isis will:

4.2.1. **Licensed Know-How – Generally**. Deliver to Roche copies of Licensed Know-How (other than the Isis Manufacturing and Analytical Know-How) in the Field in Isis' possession not previously provided hereunder, for use solely in accordance with the license granted under Section 4.1.1 to Roche together with all regulatory documentation (including drafts) related to Products. To assist with the transfer of such Licensed Know-How, Isis will make its personnel reasonably available to Roche during normal business hours to transfer such Licensed Know-How under this Section 4.2.1.

4.2.2. **Isis Manufacturing and Analytical Know-How**. Deliver, at Roche's election, to one of either (i) Roche, or (ii) a Licensed CMO solely to Manufacture API on Roche's behalf, copies of the Isis Manufacturing and Analytical Know-How relating to Products in Isis' possession not previously provided hereunder, which is necessary for the exercise by Roche, its Affiliates or a Third Party of the Manufacturing rights granted under Section 4.1.1.

4.2.3. **Technology Transfer Costs**. Isis will perform the technology transfer activities under this Section 4.2 for up to [***] FTE hours (free of charge to Roche) of Isis' time. Thereafter, if requested by Roche, Isis will provide Roche with a reasonable level of assistance in connection with such transfer, which Roche will reimburse Isis for Isis' time incurred in providing such assistance at Isis' FTE rate, and any of Isis' reasonable travel expenses for travel requested by Roche, and any outside consultants' costs and consultants' reasonable travel expenses incurred by Isis agreed in advance by Roche.

ARTICLE 5.
DEVELOPMENT, MANUFACTURING AND COMMERCIALIZATION

5.1. **Roche Diligence**. After Option exercise, subject to the terms of this Agreement, Roche is solely responsible for all Development, Manufacturing and Commercialization activities, and for all costs and expenses associated therewith, with respect to the Development, Manufacture and Commercialization of Products. Roche will use Commercially Reasonable Efforts to Develop, Manufacture and Commercialize Products, including to meet the timelines and milestones set forth in the Isis Development Candidate-R&D Plan, the IDCP and the Specific Performance Milestone Events.

Prior to Initiation of the first Registration-Directed Trial for a given Product, Roche will prepare a Development and global integrated development and commercialization plan ("***IDCP***") outlining key aspects for Developing such Product through Approval, and Roche's worldwide strategy to launch and Commercialize such Product. The IDCP will incorporate and replace the applicable R&D Plan and will take the form of, and contain information consistent with, Roche's Development and Commercialization plans for its similar products at similar stages of development or commercialization, including Product Sales forecasts. Once Roche has prepared such plan, Roche will update the IDCP consistent with Roche's standard practice and provide such updates to Isis at least Annually.

5.1.1. **Independent Expert**. After Option exercise, Roche will have the final decision-making authority regarding which Product to [***], and Roche will present its decision to the JSC. If Roche decides to progress the [***], and the JSC does not unanimously agree with Roche's decision to do so, the JSC will appoint a single, independent Third Party expert ("***Independent Expert***") mutually agreed upon by the Parties with appropriate expertise and professional credentials to evaluate Roche's decision. Each Party will have the opportunity to present its position to the Independent Expert. The Independent Expert, when considering its recommendation, will consider such factors as [***], available clinical and pre-clinical data for [***], the commercial potential of the Development Candidates and the competitive environment. The Independent Expert will make his or her own recommendation to the JSC regarding whether the Brain Shuttle Development Candidate or the Isis Development Candidate should [***]. Roche will not be required to adopt the Independent Expert's recommendation. If the Independent Expert recommends that the [***], then Roche will pay Isis the royalty rate under TABLE 4 of Section 6.7.1 applicable to [***]. If the Independent Expert recommends that the [***], Roche will pay the costs of the Independent Expert. If the Independent Expert recommends that the [***], Roche and Isis will each pay 50% of the costs of the Independent Expert.

5.1.2. **Phase 2 Trials**. The Phase 2 Trial for the first Isis Development Candidate will be designed in accordance with the Phase 2 Trial design set forth in the Isis Development Candidate-R&D Plan, taking into consideration the results of the Phase 1 Trial. The Phase 2 Trials for all other Development Candidates will be designed in accordance with the applicable R&D Plan. Roche will keep Isis informed of the progress and status of each Phase 2 Trial. Roche will notify Isis in writing promptly after Roche completes a Phase 2 Trial under the applicable R&D Plan. Promptly after such notice, once the data generated under the statistical analysis plan for a Phase 2 Trial is available to Roche, Roche will provide such data to Isis.

5.1.3. **Registration-Directed Trials**. The Registration-Directed Trials will be designed in accordance with the Registration-Directed Trial designs set forth in the applicable IDCP. Roche will keep Isis informed of the progress and status of each Registration-Directed Trial. Roche will notify Isis in writing promptly after Roche completes each Registration-Directed Trial under the applicable IDCP. Promptly after such notice, once the data generated under the statistical analysis plan for a Registration-Directed Trial is available to Roche, Roche will provide such data to Isis.

5.1.4. **Investigator's Brochure**. After Option Exercise, in addition to the IDCP, Roche will keep Isis reasonably informed with respect to the status, activities and progress of Development of Products by providing updated versions of the Investigator's Brochure to Isis Annually and upon any substantive change to the safety or risk of the Products.

5.1.5. **Participation in Regulatory Meetings**. Each Party will provide the other Party with as much advance written notice as practicable of any meetings such Party has or plans to have with a Regulatory Authority regarding pre-approval or Approval matters for a Product, and will allow the other Party (at such other Party's own expense) to participate in any such meetings as an observer.

5.1.6. **Regulatory Communications**. Each Party will provide the other Party with copies of documents and communications submitted to and received from Regulatory Authorities that materially impact the Development or Commercialization of Products for the other Party's review and comment, and the submitting Party will consider in good faith including any comments provided by the reviewing Party to such documents and communications.

5.1.7. **Participation in Roche Clinical Development Team Meetings**. [***], Roche will permit Isis to participate in Roche's key clinical development team meetings for Products (i.e., meetings that are likely to have a material impact on the Development of the Product(s)) (each such meeting, a "***Key Meeting***"), at Isis' reasonable request. Isis' and Roche's respective designated clinical leaders will work together to come up with a schedule of such Key Meetings, giving Isis as much advance written notice as practicable so that Isis may, at Isis' expense, plan for its participation in such meetings.

5.1.8. **Class Generic Claims**. If Roche intends to make any claims in a Product label or regulatory filing that are class generic to ASOs or Isis' chemistry platform(s), Roche will provide such claims and regulatory filings to Isis in advance and will consider in good faith any proposals and comments made by Isis.

5.1.9. **Applicable Laws**. Roche will perform its activities pursuant to this Agreement in compliance with applicable good laboratory and clinical practices and cGMP.

5.2. **IND; Global Safety Database.**

5.2.1. **IND**. The Parties acknowledge that until the first Development Candidate completes a Phase 1 Trial, Isis will be the holder of the IND for such Development Candidate. After Option exercise, upon transfer of Isis' Development Candidate IND to Roche and assumption by Roche of regulatory responsibilities under the IND, Roche will assume responsibility for the global safety database related to such Development Candidate. After Option exercise, Roche will be solely responsible for reporting to Regulatory Authorities in accordance with the Applicable Law for expeditable adverse events and for periodic safety reporting relating to the safety of such Development Candidate and all subsequent Development Candidates and will furnish copies of such reports to Isis.

5.2.2. Isis' Antisense Safety Database.

(a) Isis maintains an internal database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during pre-clinical and clinical development (the "***Isis Internal ASO Safety Database***"). In an effort to maximize understanding of the safety profile and pharmacokinetics of Isis compounds, after Option exercise, Roche will cooperate in connection with populating the Isis Internal ASO Safety Database. To the extent collected by Roche and in the form in which Roche uses/stores such information for its own purposes, Roche will make available to Isis information concerning toxicology, pharmacokinetics, safety pharmacology study(ies), serious adverse events and other safety information related to Products as soon as practicable following the date such information is available to Roche (but Roche will make such information available to Isis starting no later than thirty (30) days after Roche's receipt of such information). In connection with any reported serious adverse event, Roche will provide Isis all serious adverse event reports, including initial, interim, follow-up, amended, and final reports. In addition, with respect to Products, Roche will make available to Isis copies of Annual safety updates filed with each IND and the safety sections of any final Clinical Study reports within thirty (30) days following the date such information is filed or is available to Roche, as applicable. Furthermore, Roche will promptly make available to Isis any supporting data and answer any follow-up questions reasonably requested by Isis. All such information disclosed by Roche to Isis will be Roche Confidential Information; *provided*, *however*, that Isis may disclose any such Roche Confidential Information to (i) Isis' other partners pursuant to Section 5.2.2(b) below if such information is regarding class generic properties of ASOs, or (ii) any Third Party, in each case, so long as Isis does not disclose the identity of a Product or Roche. Roche will contact Isis' Chief Medical Officer at Isis Pharmaceuticals, Inc., 2855 Gazelle Court, Carlsbad, California 92010 (or at such other address/contact designated in writing by Isis) for matters related to the Isis Internal ASO Safety Database. Roche will also cause its Affiliates and Sublicensees to comply with this Section 5.2.2(a).

(b) Isis utilizes the information in the Isis Internal ASO Safety Database to conduct analyses to keep Isis and its partners informed regarding class generic properties of ASOs, including with respect to safety. As such, if and when Isis identifies safety or other related issues that may be relevant to a Product (including any potential class-related toxicity), Isis will promptly inform Roche of such issues and, if requested, provide the data supporting Isis' conclusions.

ARTICLE 6.
FINANCIAL PROVISIONS

6.1. **Option Fee**. In partial consideration for Roche's Option hereunder, within ten (10) days following the Effective Date and receipt by Roche of an invoice from Isis, Roche will pay Isis an Option fee equal to thirty million dollars (US$30,000,000).

6.2. **Milestone Payments for Achievement of Pre-Licensing Milestone Events**. As further consideration for Roche's Option, Roche will pay to Isis the milestone payments as set forth in TABLE 1 below when a milestone event (each, a "***Pre-Licensing Milestone Event***") listed in TABLE 1 is first achieved by the applicable Development Candidate:

TABLE 1			
Pre-Licensing Milestone Events	**Column 1 Milestone Payments for the Isis Development Candidate to First Achieve Milestone Event**	**Column 2 Milestone Payments for Additional Isis Development Candidate to Achieve Milestone Event**	**Column 3 Milestone Payments for First Brain Shuttle Development Candidate to Achieve Milestone Event**
[***]	[***]	[****]	[***]
[***]	[***]	[***]	[***†]

*[***] milestone payment is only payable once in accordance with Section 1.8.1(b).

†This milestone payment is not payable by Roche if Roche has already paid Isis the [***] milestone payment under Column 1 of this TABLE 1.

Except for the [***] milestone payment in Column 2 of TABLE 1 for an Additional Isis Development Candidate, Roche will pay to Isis the Milestone Event payments as set forth in TABLE 1 after the applicable Milestone Event is first achieved by a Development Candidate even if Roche has exercised the Option prior to achievement of the Milestone Event.

6.3. **License Fee**. Pursuant to Section 3.2, subsequent to Roche's written notice to exercise its Option in accordance with this Agreement, Roche will pay to Isis a license fee of [***] within thirty (30) days after providing such written notice and receipt by Roche of an invoice from Isis.

6.4. **Milestone Payments for Achievement of Post-Licensing Milestone Events**. Roche will pay Isis the milestone payments set forth in TABLE 2 below when a milestone event (each, a "***Post-Licensing Milestone Event***") listed in TABLE 2 is first achieved by a Product:

TABLE 2		
Post-Licensing Milestone Event	**Column 1 Milestone Payment for First Product to Achieve Milestone Event**	**Column 2 Milestone Payment for Each Product After the First Product to Achieve Milestone Event**
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]

6.5. **Milestone Payments for First Achievement of Sales Milestone Event**. Roche will pay Isis the applicable one-time milestone payments set forth in TABLE 3 below after the first achievement of the listed events, by or on behalf of Roche or its Affiliates or Sublicensees. For clarity, notwithstanding any provision to the contrary in this Agreement, any consideration received by Roche or its Affiliates from a Compulsory Sublicensee for the sale of Products in a given Calendar Year will be added to Net Sales of Products for such year for purposes of determining whether any of the Sales Milestones in TABLE 3 have been achieved.

TABLE 3	
Sales Milestone	**Sales Milestone Payment**
[***] in aggregate worldwide Annual Net Sales of Products comprising an Isis Development Candidate	[***]
[***] in aggregate worldwide Annual Net Sales of Products comprising an Isis Development Candidate	[***]
[***] in aggregate worldwide Annual Net Sales of Products comprising a Brain Shuttle Development Candidate	[***]
[***] in aggregate worldwide Annual Net Sales of Products comprising a Brain Shuttle Development Candidate	[***]
Total Sales Milestone Payments	[***]

6.6. Limitations on Milestone Payments; Exceptions; Notice.

6.6.1. Each milestone payment set forth in TABLE 1, and in Column 1 of TABLE 2 above, will be paid only once upon the first achievement of the Milestone Event regardless of how many times such Milestone Event is achieved. On a Product-by-Product basis, each milestone payment set forth in Column 2 of TABLE 2 above will be paid only once upon the first achievement of the Milestone Event by the applicable Product. Each milestone payment set forth in TABLE 3 above will be paid only once upon the first achievement of the Milestone Event.

6.6.2. If a particular Milestone Event is not achieved because Development activities transpired such that achievement of such earlier Milestone Event was unnecessary or did not otherwise occur, then upon achievement of a later Milestone Event the Milestone Event payment applicable to such earlier Milestone Event will also be due. For example, if a Party proceeds directly to [***] without achieving the [***] then upon achieving the [***] Milestone Event, both the [***] and [***] Milestone Event payments are due.

6.6.3. Each time a Milestone Event is achieved under this ARTICLE 6, the Party that achieved such Milestone Event will send to the other Party a written notice thereof promptly (but no later than ten (10) Business Days) following the date of achievement of such Milestone Event and such payment will be due within thirty (30) days of the date such Milestone Event was achieved and receipt of an invoice by Roche from Isis.

6.7. Royalty Payments to Isis.

6.7.1. **Roche Full Royalty**. As partial consideration for the rights granted to Roche hereunder, subject to the provisions of this Section 6.7.1 and Section 6.7.2, Roche will pay to Isis royalties on Annual worldwide Net Sales of Products sold by Roche, its Affiliates or Sublicensees, on a country-by-country and Product-by-Product basis, in each case in the amounts as follows in TABLE 4 below (the "***Roche Full Royalty***"):

TABLE 4

Royalty Tier	Annual Worldwide Net Sales	Royalty Rate for Products Comprising: Isis Development Candidate	Brain Shuttle Development Candidate	Roche-Selected Brain Shuttle Development Candidate
1	For the portion of Annual Worldwide Net Sales < $[***]	[***]%	[***]%	[***]%
2	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%	[***]%	[***]%
3	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%	[***]%	[***]%
4	For the portion of Annual Worldwide Net Sales ≥ $[***]	[***]%	[***]%	[***]%

(a) Annual worldwide Net Sales for a particular Product will be calculated by [***]. For clarity, notwithstanding any provision to the contrary in this Agreement, any consideration received by Roche or its Affiliates from a Compulsory Sublicensee solely for the sale of Products in a given Calendar Year will be added to Net Sales of Products for such year for purposes of determining which royalty tier (and therefore which royalty rate) applies to a particular Product in TABLE 4.

(b) Roche will pay Isis royalties on Net Sales of Products arising from named patient and other similar programs under Applicable Laws, and Roche will provide reports and payments to Isis consistent with Section 6.12. No royalties are due on Net Sales of Products arising from compassionate use and other programs providing for the delivery of Product at no cost. The sales of Products arising from named patient, compassionate use or other similar programs will not be considered a First Commercial Sale for purposes of determining the Full Royalty Period.

6.7.2. **Application of Royalty Rates**. All royalties set forth under Section 6.7.1 are subject to the provisions of this Section 6.7.2, and are payable as follows:

(a) **Full Royalty Period**. Roche's obligation to pay Isis the Roche Full Royalty above with respect to a Product will continue on a country-by-country and Product-by-Product basis from the date of First Commercial Sale of such Product until the later of the date of expiration of (i) the last Valid Claim within the Licensed Patents or the Brain Shuttle Collaboration Patents Covering such Product in the country in which such Product is used or sold, (ii) the data exclusivity period conferred by the applicable Regulatory Authority in such country with respect to such Product (e.g., such as in the case of an orphan drug), or (iii) the [***] anniversary of the First Commercial Sale of such Product in such country; *provided*, *however*, that, on a country-by-country and Product-by-Product basis, if neither of the periods set forth in clause (i) and clause (ii) of this Section 6.7.2(a) apply to a Product, then the Roche Full Royalty will continue to apply through the [***] anniversary of the First Commercial Sale of such Product in such country ***unless*** a [***] in such country, at which time in lieu of paying the Roche Full Royalty, Roche will pay Isis the Roche Reduced Royalty for such Product in such country in accordance with Section 6.7.2(b) (such royalty period, the "***Full Royalty Period***"). For clarity, (X) Licensed Patents that are jointly-owned by Roche, and (Y) Brain Shuttle Collaboration Patents that are jointly or solely-owned by Roche or its Affiliates, will count toward the calculation of the Full Royalty Period in a particular country if the use or sale of a Product by an unauthorized Third Party in such country would infringe a Valid Claim of such Licensed Patent or Brain Shuttle Collaboration Patent.

(b) **Reduced Royalty Period**. Subject to Section 6.7.2(c), on a country-by-country and Product-by-Product basis, after the expiration of the Full Royalty Period in a country and until the end of the Reduced Royalty Period, in lieu of the royalty rates set forth in TABLE 4 of Section 6.7.1, Roche will pay Isis royalty rates (the "***Roche Reduced Royalty***") on Net Sales of Products in such country calculated on a Calendar Quarter-by-Calendar Quarter basis by [***]; *provided*, *however*, that the Roche Reduced Royalty rate in each country will in no event exceed the Reference Rate applicable under this Section 6.7. For example, if peak Calendar Year Net Sales of a Product comprising an Isis Development Candidate during the Full Royalty Period were [***] and royalties paid for that same Calendar Year were [***] resulting in a [***], and if [***] and the [***], the applicable [***] in such country would be [***]. Similarly, if the quarterly [***], then the applicable [v] in such country would be [***].

(c) **Limitation on Aggregate Reduction for Roche Royalties**.

(i) In no event will the aggregate royalty reductions under Section 6.7.2(b) and/or Section 6.8 reduce the royalties payable to Isis on Net Sales of a Product in any given period to an amount that is less than the [***].

(ii) In no event will the aggregate royalty offsets under Section 6.11.3(b) reduce the royalties payable to Isis on Net Sales of a Product in any given period to an amount that is less than the greater of (i) [***], and (ii) [***].

(d) **End of Royalty Obligation**. On a country-by-country basis, other than [***], Roche's obligation to make royalty payments hereunder in such country will end on the expiration of the Reduced Royalty Period in such country. "***Reduced Royalty Period***" means, on a country by country basis, the period commencing upon the expiration of the [***] in such country and ending when the [v] (i) with respect to Net Sales of Products in Major Markets, [***], and (ii) [***].

(e) **Royalty Examples**. SCHEDULE 6.7.2(e) attached hereto contains examples of how royalties will be calculated under this Section 6.7.

(f) **Allocation of Net Sales**. If, by reason of one or more royalty rate adjustments under this Section 6.7.2, different royalty rates apply to Net Sales of Products from different countries, Roche will [***] such Net Sales [***]. SCHEDULE 6.7.2(f) attached hereto contains examples of how Net Sales of Products from different countries at different royalty rates will be [***].

6.8. **Royalty Reduction Due to Decline In Product Sales Clearly Attributable to Sales of an [***].** If, after taking into account the then available data, including but not limited to epidemiology data, any Third Party product sales and diagnostics sales data and relevant market research information, Roche determines (and provides written notice to Isis of such determination and the basis therefor) that any decline in sales of the AS Development Candidate being Commercialized by Roche is clearly attributable to the sales of any [***], then, subject to Section 6.7.2(c)(i), the royalty rates under TABLE 4 applicable to such AS Development Candidate being Commercialized by Roche, its Affiliates or Sublicensees [***]. For example, if Roche determines such decline in sales to be [***], then Roche shall reduce royalties otherwise payable to Isis based on the actual Net Sales for that Calendar Quarter [***]. If Roche implements a royalty reduction under this Section 6.8, Roche will make such reductions with a one Calendar Quarter delay in order to generate the data and supporting calculations necessary to determine the amount of any such reduction, and Roche shall include its calculation of such reduction in the applicable royalty report under Section 6.12.2. If Isis believes that any decline in sales of the AS Development Candidate being Commercialized by Roche is not clearly attributable to the sales of any such [***], the Parties will discuss the matter in good faith and if the Parties cannot resolve such matter it will be resolved in accordance with the dispute resolution process set forth in Section 12.1. Roche is not entitled to any royalty reduction under this Section 6.8 as a result of sales of [***].

6.9. **Apportionment of Compulsory Sublicensee Consideration**. At such time as Roche or any of its Affiliates or Sublicensees enters into a sublicense with a Compulsory Sublicensee, the Parties will discuss and mutually agree upon an adjustment of the royalty due to Isis under Section 6.7 of this Agreement with respect to sales of Products by such Compulsory Sublicensee, with such adjustment calculated based on a [***].

6.10. **Reverse Royalty Payments to Roche for Discontinued Products**.

6.10.1. **Reverse Royalty for a Discontinued Product Comprising an Isis Development Candidate**. If Isis or any of its Affiliates or Sublicensees Commercializes a Discontinued Product for which Roche has paid Isis the license fee under Section 6.3 and such Discontinued Product (i) is comprised of an Isis Development Candidate, and (ii) was not commercialized by Roche, its Affiliates or its Sublicensees, then following the First Commercial Sale of such Discontinued Product by Isis or its Affiliates or Sublicensees, Isis will pay Roche a royalty of [***] of Annual worldwide net sales of such Discontinued Product ("***Isis Development Candidate Reverse Royalties***"). Isis will pay Roche such Isis Development Candidate Reverse Royalties in accordance with the provisions governing payment of royalties from Roche to Isis in Sections 6.7.2, 6.11, 6.12, 6.13, 6.14, and 6.15 (*mutatis mutandis*); *provided, however*, that Isis' obligation to pay Roche Isis Development Candidate Reverse Royalties will expire once Isis has paid Roche an amount equal to [***] for such Discontinued Product under Section 6.2 and Section 6.4.

6.10.2. **Reverse Royalty for a Discontinued Product Comprising a Brain Shuttle Development Candidate**. If Roche has paid Isis the license fee under Section 6.3 and Isis or any of its Affiliates or Sublicensees Commercializes a Discontinued Product that is comprised of a Brain Shuttle Development Candidate, then following the First Commercial Sale of such Discontinued Product by Isis or its Affiliates or Sublicensees, Isis will pay Roche a royalty of [***] of Annual worldwide net sales of such Discontinued Product ("***Brain Shuttle Development Candidate Reverse Royalties***"). Isis will pay Roche Brain Shuttle Development Candidate Reverse Royalties in accordance with (and for the same duration as) the provisions governing payment of royalties from Roche to Isis in Sections 6.7.2, 6.11, 6.12, 6.13, 6.14, and 6.15, *mutatis mutandis*.

6.11. **Third Party Payment Obligations**.

6.11.1. **Existing In-License Agreements**.

(a) ***Isis' Existing In-License Agreements***. Certain of the Licensed Technology Controlled by Isis as of the Effective Date licensed to Roche under Section 4.1.1 are in-licensed or were acquired by Isis under the agreements with Third Party licensors or sellers listed on SCHEDULE 6.11.1 (such license or purchase agreements being the "***Isis In-License Agreements***"), and certain milestone or royalty payments and license maintenance fees may become payable by Isis to such Third Parties under the Isis In-License Agreements based on the Development or Commercialization of a Product by Roche under this Agreement. Any payment obligations arising under the Isis In-License Agreements as they apply to Products that:

(i) accrue prior to Option exercise, will be paid by [***] as [***]; and

(ii) accrue after Option exercise, will be paid by [v] as [***].

(b) ***Isis' Agreements at the time of Option Exercise.*** Prior to Roche exercising the Option, Isis shall disclose to Roche all agreements (other than the In-License Agreements) entered into after the Effective Date by Isis with Third Party licensors or sellers under which Isis licensed or acquired any Licensed Technology to be licensed to Roche under Section 4.1.1 ("***Additional Isis In-License Agreements***"). Any payment obligations arising under any Additional Isis In-License Agreements as they apply to Products that:

(i) accrue prior to Option exercise, will be paid by [***] as [***]; and

(ii) accrue after Option exercise, will be paid by [***] as [***], in which case Section 6.11.3 will apply.

(c) ***Roche's Existing In-License Agreements***. Roche will be solely responsible for any Third Party Obligations that become payable by Roche to Third Parties under any agreements or arrangements Roche has with such Third Parties as of the Effective Date, based on the Development or Commercialization of a Product by Roche, its Affiliate or Sublicensee under this Agreement. Any such payment obligations will be paid by [***] as [***] under this Agreement.

6.11.2. **New In-Licensed Product-Specific Patents**.

(a) On a Product-by-Product basis, after Option exercise, Roche or Isis, as the case may be, will promptly provide the other Party written notice of any additional Third Party Patent Rights it has identified as necessary to Develop or Commercialize a Product where such Third Party Patent Rights would be considered a Product-Specific Patent if either Party Controlled such Patent Rights ("***Additional Product-Specific Patents***"), and Roche will have the first right, but not the obligation, to negotiate with, and obtain a license from the Third Party Controlling such Additional Product-Specific Patents. If Roche obtains any such Additional Product-Specific Patents then any financial obligations under such Third Party agreement will be paid solely by [***] as [***].

(b) If, however, Roche elects not to obtain such a license to such Additional Product-Specific Patents, Roche will so notify Isis, and Isis may obtain such a license to such Additional Product-Specific Patents and Isis will include such Additional Product-Specific Patents in the license granted to Roche under Section 4.1.1 provided that Roche agrees in writing to [***].

6.11.3. Additional Core IP In-License Agreements.

(a) Roche will promptly provide Isis written notice of any [***] ("***Additional Core IP***") that Roche believes it has identified and Isis will have the first right, but not the obligation, to negotiate with, and obtain a license from the Third Party Controlling such Additional Core IP. For clarity, Additional Core IP does not include any Patent Rights claiming (or intellectual property related to) [***]. If Isis obtains such a Third Party license, Isis will include such Additional Core IP in the license granted to Roche under Section 4.1.1, and any financial obligations under such Third Party agreement will be paid solely by [***] as [***].

(b) If, however, Isis elects not to obtain such a license to such Third Party intellectual property, Isis will so notify Roche, and Roche may obtain such a Third Party license and, subject to Section 6.7.2(c)(ii), Roche may offset an amount equal to [***] of [***] paid by Roche under such Third Party license against any [***] of this Agreement in such country for [***].

(c) If Isis does not agree with Roche that a license to such Third Party Patent Rights is necessary to [***], then Isis will send written notice to such effect to Roche, and the Parties will engage a mutually agreed independent Third Party intellectual property lawyer with expertise in the patenting of ASOs, and appropriate professional credentials in the relevant jurisdiction, to determine the question of whether or not such Third Party intellectual property is Additional Core IP. The determination of the Third Party expert engaged under the preceding sentence will be binding on the Parties solely for purposes of determining whether Roche is permitted to [***]. The costs of any Third Party expert engaged under this Section 6.11.3(c) will be paid by the Party against whose position the Third Party lawyer's determination is made.

6.12. Payments.

6.12.1. Commencement. Beginning with the Calendar Quarter in which the First Commercial Sale, named patient sale, compassionate use sale or other similar sales for a Product is made and for each Calendar Quarter thereafter, Roche will make royalty payments to Isis under this Agreement within [***] following the end of each such Calendar Quarter.

6.12.2. Royalty Reporting. Each royalty payment will be accompanied by a report, summarizing in writing for the relevant Calendar Quarter on a Product-by-Product basis the following information:

(a) Sales in Swiss Francs on a country-by-country basis;

(b) Net Sales in Swiss Francs on a country-by-country basis;

(c) Total worldwide Net Sales in Swiss Francs;

(d) Exchange rate used for the conversion of Net Sales from Swiss Francs to US Dollars pursuant to Section 6.12.4;

(e) Royalty Rate pursuant to Section 2.1.1(b)(ii) (if applicable), Section 6.7.1 and Section 6.7.2, as applicable; and

(f) Total Royalty payable in US Dollars.

In addition, Roche will include in each report under this Section 6.12.2 information regarding any Net Sales of Products sold for named patient, compassionate use or other similar sales and any consideration received from any Compulsory Sublicensees.

6.12.3. After first Approval, if no royalties or other payments from Product sales are payable in respect of a given Calendar Quarter, Roche will submit a written royalty report to Isis so indicating together with an explanation as to why no such royalties are payable. In addition, beginning with the Calendar Quarter in which the First Commercial Sale for a Product (or any named patient sale, compassionate use sale or other similar sales of a Product) is made and for each Calendar Quarter thereafter, within ten (10) Business Days following the end of each such Calendar Quarter, Roche will provide Isis a [***] report estimating the total (A) Sales and Net Sales for Products projected for such Calendar Quarter, and (B) if available, the amount of any consideration payable to Roche under sublicenses with Compulsory Sublicensees.

6.12.4. **Mode of Payment**. All payments under this Agreement will be (i) payable in full in U.S. Dollars, regardless of the country(ies) in which sales are made, (ii) made by wire transfer of immediately available funds to an account designated by Isis in writing, and (iii) irrevocable and non-refundable. Any corrections to calculations of royalty payments previously paid shall be adjusted to the next royalty payment due. When calculating the Sales of a Product that occur in currencies other than U.S. Dollars, Roche will convert the amount of such sales into Swiss Francs and then into U.S. Dollars using Roche's then current internal foreign currency translation actually used on a consistent basis in preparing its audited financial statements (currently YTD average rate as reported by Reuters).

6.12.5. **Records Retention**. Commencing with the First Commercial Sale or named patient sale of a Product, Roche will keep complete and accurate records pertaining to the sale of Products for a period of [***] after the year in which such sales occurred, and in sufficient detail to permit Isis to confirm the accuracy of the Net Sales or royalties paid by Roche hereunder.

6.13. **Audits**. After the first Approval of a Product, during the remaining Agreement Term and for a period of thirty-six (36) calendar months thereafter, at the request and expense of Isis, Roche will permit an independent certified public accountant of internationally recognized standing appointed by Isis, at reasonable times and upon at least sixty (60) Business Days written notice, but in no case more than once per Calendar Year, to examine such records as may be necessary for the purpose of verifying the calculation and reporting of Net Sales and the correctness of any royalty payment made under this Agreement for any period within the preceding thirty-six (36) calendar months. No Calendar Year can be audited more than once. Any and all records of Roche examined by such independent certified public accountant will be deemed Roche's Confidential Information. The independent certified public accountant shall share all draft reports with Roche before the draft audit report is shared with Isis and before the final document is issued. Upon completion of the audit, the accounting firm will provide both Roche and Isis with a written report disclosing whether the royalty payments made by Roche are correct and the specific details concerning any discrepancies ("***Audit Report***"). If, as a result of any inspection of the books and records of Roche, it is shown that Roche's payments under this Agreement were less than the royalty amount that should have been paid, then Roche will make all payments required to be made by paying Isis the difference between such amounts to eliminate any discrepancy revealed by said inspection with the next royalty payment due, with interest calculated in accordance with Section 6.15. If, as a result of any inspection of the books and records of Roche, it is shown that Roche's payments under this Agreement were greater than the royalty amount that should have been paid, then [***]. Isis will pay all fees charged by such accountant pursuant to the audit, *except that*, if the audit determines that any additional amounts payable by Roche for an audited period exceed [***] of the amount actually paid for such audited period, then, in addition to paying Isis any unpaid amounts discovered in such audit, Roche will pay the fees and expenses charged by such accountant.

6.14. **Taxes**.

6.14.1. **Taxes on Income**. Each Party will be solely responsible for the payment of all taxes imposed on its share of income arising directly or indirectly from the activities of the Parties under this Agreement.

6.14.2. **Withholding Tax**. To the extent the paying Party is required to deduct and withhold taxes on any payment, the paying Party will pay the amounts of such taxes to the proper governmental authority for the account of the receiving Party and remit the net amount to the receiving Party in a timely manner. The paying Party will promptly furnish the receiving Party with proof of payment of such taxes. If documentation is necessary in order to secure an exemption from, or a reduction in, any withholding taxes, the Parties will provide such documentation to the extent they are able to do so. In accordance with the procedures set forth in Section 9.3, the receiving Party will also indemnify the paying Party for any tax, interest or penalties imposed on the paying Party if the paying Party improperly reduces or eliminates withholding tax based upon representations made by the receiving Party.

6.14.3. **Tax Cooperation**. At least fifteen (15) days prior to the date a given payment is due under this Agreement, the non-paying Party will provide the paying Party with any and all tax forms that may be reasonably necessary in order for the paying Party to lawfully not withhold tax or to withhold tax at a reduced rate with respect to such payment under an applicable bilateral income tax treaty. Following the paying Party's timely receipt of such tax forms from the non-paying Party, the paying Party will not withhold tax or will withhold tax at a reduced rate under an applicable bilateral income tax treaty, if appropriate under the Applicable Laws. The non-paying Party will provide any such tax forms to the paying Party upon request and in advance of the due date. Each Party will provide the other with reasonable assistance to enable the recovery, as permitted by Applicable Law, of withholding taxes resulting from payments made under this Agreement, such recovery to be for the benefit of the Party who would have been entitled to receive the money but for the application of withholding tax under this Section 6.14.

The provisions of this Section 6.14 are to be read in conjunction with the provisions of Section 12.4 below.

6.15. **Interest**. Any undisputed payments to be made hereunder that are not paid on or before the date such payments are due under this Agreement will bear interest at a rate per annum equal to the lesser of (i) one month LIBOR rate in effect on the date that such payment would have been first due plus two percentage points (2%) or (ii) the maximum rate permissible under applicable law.

ARTICLE 7.
INTELLECTUAL PROPERTY

7.1. **Ownership**.

7.1.1. **Isis Technology and Roche Technology**. As between the Parties, Isis will own and retain all of its rights, title and interest in and to the Licensed Know-How and Licensed Patents and Roche will own and retain all of its rights, title and interest in and to the Roche Know-How and Roche Patents, subject to any assignments, rights or licenses expressly granted by one Party to the other Party under this Agreement.

7.1.2. **Agreement Technology**. Each Party will promptly disclose to the other Party in writing, and will cause its Affiliates to so disclose, the discovery, development, or creation of any invention made solely or jointly by the Parties in connection with the performance of obligations under this Agreement. Except as expressly provided in this Agreement, neither Party will have any obligation to account to the other for profits with respect to, or to obtain any consent of the other Party to license or exploit, Jointly-Owned Collaboration Technology by reason of joint ownership thereof, and each Party hereby waives any right it may have under the laws of any jurisdiction to require any such consent or accounting.

7.1.3. Joint Patent Committee.

(a) The Parties will establish a "***Joint Patent Committee***" or "***JPC***." The JPC will serve as the primary contact and forum for discussion between the Parties with respect to intellectual property matters arising under this Agreement, and will cooperate with respect to the activities set forth in this ARTICLE 7. Isis' obligation to participate in the JPC will terminate upon the date Isis is no longer obligated to participate in the JSC. Thereafter, Isis will have the right, but not the obligation, to participate in JPC meetings. The JPC determines the invention classification for each invention arising under this Agreement. The classifications are (i) Brain Shuttle Collaboration Patents, (ii) Isis Product-Specific Patents, (iii) Jointly-Owned Collaboration Patents, (iv) Isis Core Technology Patents, and (v) Isis Manufacturing and Analytical Patents. In addition, with respect to the Brain Shuttle Collaboration Patents classification, the JPC will determine the following sub-categories of Brain Shuttle Collaboration Patents: (w) Patent Rights claiming inventions solely related to the Brain Shuttle Technology ("***Brain Shuttle-Specific Collaboration Patents***"); (x) Patent Rights claiming inventions solely related to ASOs that do not utilize the Brain Shuttle Technology ("***ASO-Specific Collaboration Patents***"); (y) Patent Rights claiming inventions solely related to the linking or conjugation of molecules ("***Linker-Specific Collaboration Patents***"); and (z) Patent Rights claiming more than one of the technologies described in items (w) through (y) above ("***Omnibus Collaboration Patents***"). The JPC will endeavor to separate the claims within such Patent Rights into separate and distinct patent applications corresponding with the categories and sub-categories described in this Section 7.1.3(a) to the extent possible without diminishing the patentability of the inventions.

(b) A strategy will be discussed with regard to (x) prosecution and maintenance, defense and enforcement of (A) Brain Shuttle Collaboration Patents, (B) Isis Product-Specific Patents, and (C) Jointly-Owned Collaboration Patents licensed to Roche under Section 4.1.1 in connection with a Product, (y) defense against allegations of infringement of Third Party Patent Rights, and (z) licenses to Third Party Patent Rights or Know-How (including whether to obtain any licenses under any such Third-Party Patent Rights or Know-How, and whether there are any known Third Party Obligations applicable to a particular Product), in each case to the extent such matter would be reasonably likely to have a material impact on the Agreement or the licenses granted hereunder, which strategy will be considered in good faith by the Party entitled to prosecute, enforce and defend such Patent Rights hereunder, but will not be binding on such Party. Notwithstanding the above, subject to the provisions of Section 6.11, Roche shall have final say as to whether to obtain any licenses under Third-Party Patent Rights or Know-How.

(c) In addition, the Joint Patent Committee will be responsible for the determination of inventorship. The determination of inventorship will be in accordance with United States patent laws and therefore will determine if the invention is solely or jointly owned by the relevant Party or Parties. In case of a dispute in the Joint Patent Committee (or otherwise between Isis and Roche) over inventorship or classification, if the Joint Patent Committee cannot resolve such dispute, even after seeking the JSC's input, such dispute will be resolved by independent patent counsel not engaged or regularly employed in the past two years by either Party and reasonably acceptable to both Parties. The decision of such independent patent counsel will be binding on the Parties. Expenses of such patent counsel will be shared equally by the Parties.

(d) The JPC will comprise an equal number of members from each Party. The Joint Patent Committee will meet as often as agreed by them (and at least semi-Annually), to discuss matters arising out of the activities set forth in this ARTICLE 7. The JPC will determine by unanimous consent the JPC operating procedures at its first meeting. To the extent reasonably requested by either Party, the Joint Patent Committee will solicit the involvement of more senior members of their respective legal departments with respect to critical issues. Each Party's representatives on the Joint Patent Committee will consider comments and suggestions made by the other in good faith. If either Party deems it reasonably advisable, the Parties will enter into a mutually agreeable common interest agreement covering the matters contemplated by this Agreement.

7.2. Prosecution and Maintenance of Patents.

7.2.1. Patent Filings. The Party responsible for Prosecution and Maintenance of any Patent Rights as set forth in Section 7.2.2 and Section 7.2.3 will endeavor to obtain patent protection for a Product as it Prosecutes and Maintains its other patents Covering products in development, using counsel of its own choice but reasonably acceptable to the other Party, in such countries as the responsible Party sees fit.

7.2.2. Licensed Patents and Roche Patents.

(a) Licensed Patents.

(i) Isis Core and Manufacturing Patents. Isis will at all times control and be responsible for all aspects of (i) any Brain Shuttle Collaboration Patents solely-owned by Isis that (A) include claims that are directed to subject matter applicable to ASOs in general, or (B) include an ASO, the sequence of which targets the RNA that encodes HTT and ASOs that do not target the RNA encoding HTT (each, an "***Isis Core Brain Shuttle Collaboration Patent***"), (ii) the Isis Core Technology Patents, and (iii) the Isis Manufacturing and Analytical Patents.

(ii) **Isis Product-Specific Patents**.

(1) ***Before Option Exercise***. Before Option exercise, subject to Section 7.2.3 and Section 7.2.4, at Isis' expense, Isis will control and be responsible for all aspects of the Prosecution and Maintenance of all (x) Brain Shuttle Collaboration Patents solely-owned by Isis that are necessary or useful to Develop or Commercialize a Product eligible to be licensed to Roche under Section 4.1.1 and *are not* necessary or useful to develop or commercialize products that are not Products (each, an "***Isis Product-Specific Brain Shuttle Collaboration Patent***"), and (y) Isis Product-Specific Patents, and will use commercially reasonably efforts to Prosecute and Maintain such Patent Rights.

(2) ***After Option Exercise***. After Option exercise, subject to Section 7.2.3 and Section 7.2.4, at Roche's expense, Roche will control and be responsible for all aspects of the Prosecution and Maintenance of all Isis Product-Specific Brain Shuttle Collaboration Patents and Isis Product-Specific Patents Covering Products licensed to Roche under Section 4.1.1 and will either (i) use commercially reasonably efforts to Prosecute and Maintain such Patent Rights or (ii) offer to assign Roche's entire right, title and interest in such Patent Rights to Isis, in which case following any such assignment all licenses granted in this Agreement by Isis to Roche under such Patent Rights shall become non-exclusive and the exclusivity covenants under Section 2.1.1 will no longer apply to such Patent Rights.

(b) **Roche Patents and Roche Brain Shuttle Collaboration Patents**. Roche will control and be responsible for all aspects of the Prosecution and Maintenance of all (i) Brain Shuttle Collaboration Patents solely-owned by Roche, and (ii) Roche Patents, subject to Section 7.2.3 and Section 7.2.4.

7.2.3. **Jointly-Owned Collaboration Patents**.

(a) ***Before Option Exercise***. Before Option exercise, (i) Isis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Collaboration Patents Covering Isis Development Candidates, and (ii) Roche will control and be responsible for all aspects of the Prosecution and Maintenance of any Jointly-Owned Collaboration Patents Covering Brain Shuttle Development Candidates.

(b) ***After Option Exercise***. After Option exercise, Roche will control and be responsible for all aspects of the Prosecution and Maintenance of (i) Jointly-Owned Collaboration Patents Covering Products, and (ii) jointly-owned Brain Shuttle Collaboration Patents, and will either (y) use commercially reasonably efforts to Prosecute and Maintain such Patent Rights or (z) offer to assign Roche's entire right, title and interest in such Patent Rights to Isis, in which case following any such assignment all licenses granted in this Agreement by Isis to Roche under such Patent Rights shall become non-exclusive and the exclusivity covenants under Section 2.1.1 will no longer apply to such Patent Rights.

7.2.4. Other Matters Pertaining to Prosecution and Maintenance of Patents.

(a) Each Party will keep the other Party informed through the Joint Patent Committee as to material developments with respect to the Prosecution and Maintenance of the Product-Specific Patents or Jointly-Owned Collaboration Patents for which such Party has responsibility for Prosecution and Maintenance pursuant to Section 7.2.2, Section 7.2.3 or this Section 7.2.4, including by providing copies of material data as it arises, any office actions or office action responses or other correspondence that such Party provides to or receives from any patent office, including notice of all interferences, reissues, re-examinations, oppositions or requests for patent term extensions, and all patent-related filings, and by providing the other Party the timely opportunity to have reasonable input into the strategic aspects of such Prosecution and Maintenance.

(b) If Roche elects (a) not to file and prosecute patent applications for the Jointly-Owned Collaboration Patent or Isis Product-Specific Patents that have been licensed to Roche under this Agreement or the Brain Shuttle Collaboration Patents for which Roche has responsibility for Prosecution and Maintenance pursuant to Section 7.2.2 or Section 7.2.3 ("***Roche-Prosecuted Patents***") in a particular country, (b) not to continue the prosecution (including any interferences, oppositions, reissue proceedings, re-examinations, and patent term extensions, adjustments, and restorations) or maintenance of any Roche-Prosecuted Patent in a particular country, or (c) not to file and prosecute patent applications for the Roche-Prosecuted Patent in a particular country following a written request from Isis to file and prosecute in such country, then Roche will so notify Isis promptly in writing of its intention in good time to enable Isis to meet any deadlines by which an action must be taken to establish or preserve any such Patent Right in such country; and Isis will have the right, but not the obligation, to file, prosecute, maintain, enforce, or otherwise pursue such Roche-Prosecuted Patent in the applicable country at its own expense with counsel of its own choice. In such case, Roche will cooperate with Isis to file for, or continue to Prosecute and Maintain or enforce, or otherwise pursue such Roche-Prosecuted Patent in such country in Isis' own name. Notwithstanding anything to the contrary in this Agreement, if Isis assumes responsibility for the Prosecution and Maintenance of any such Roche-Prosecuted Patent under this Section 7.2.4(b), Isis will have no obligation to notify Roche if Isis intends to abandon such Roche-Prosecuted Patent. The analogous situation shall apply *mutatis mutandis* with regard to Patent Rights (excluding Isis Core Technology Patents and Isis Manufacturing and Analytical Patents) for which Isis has responsibility for Prosecution and Maintenance pursuant to Section 7.2.2 or Section 7.2.3.

(c) The Parties, through the Joint Patent Committee, will cooperate in good faith to determine if and when any divisional or continuation applications will be filed with respect to any Jointly-Owned Collaboration Patents or Product-Specific Patents, and where a divisional or continuation patent application filing would be practical and reasonable, then such a divisional or continuation filing will be made.

(d) If the Party responsible for Prosecution and Maintenance pursuant to Section 7.2.3 intends to abandon such Jointly-Owned Collaboration Patent without first filing a continuation or substitution, then such Party will notify the other Party of such intention at least sixty (60) days before such Jointly-Owned Collaboration Patent will become abandoned, and such other Party will have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense (subject to Section 7.3.1) with counsel of its own choice, in which case the abandoning Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, title and interest in and to such Jointly-Owned Collaboration Patents. If a Party assumes responsibility for the Prosecution and Maintenance of any such Jointly-Owned Collaboration Patents under this Section 7.2.4(d), such Party will have no obligation to notify the other Party of any intention of such Party to abandon such Jointly-Owned Collaboration Patents.

(e) In addition, the Parties will consult, through the Joint Patent Committee, and take into consideration the comments of the other Party for all matters relating to interferences, reissues, re-examinations and oppositions with respect to those Patent Rights in which such other Party (i) has an ownership interest, (ii) has received a license thereunder in accordance with this Agreement, or (iii) may in the future, in accordance with this Agreement, obtain a license or sublicense thereunder.

7.3. Patent Costs.

7.3.1. **Jointly-Owned Collaboration Patents**. Unless the Parties agree otherwise, Isis and Roche will share equally the Patent Costs associated with the Prosecution and Maintenance of Jointly-Owned Collaboration Patents; *provided that*, either Party may decline to pay its share of costs for filing, prosecuting and maintaining any Jointly-Owned Collaboration Patents in a particular country or particular countries, in which case the declining Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, titles and interests in and to such Jointly-Owned Collaboration Patents.

7.3.2. **Licensed Patents and Roche Patents**. Except as set forth in Section 7.2.4 and Section 7.3.1, each Party will be responsible for all Patent Costs incurred by such Party prior to and after the Effective Date in all countries in the Prosecution and Maintenance of Patent Rights for which such Party is responsible under Section 7.2; *provided*, *however*, that after Option exercise, Roche will be solely responsible for Patent Costs arising from the Prosecution and Maintenance of the Isis Product-Specific Patents; *provided that*, Roche may decline to pay for filing, prosecuting and maintaining any Isis Product-Specific Patents in a particular country or particular countries, in which case all licenses granted in this Agreement by Isis to Roche under such Patent Rights shall become non-exclusive and the exclusivity covenants under Section 2.1.1 will no longer apply to such Patent Rights.

7.4. **Defense of Claims Brought by Third Parties**.

7.4.1. If a Third Party initiates a Proceeding claiming a Patent Right owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of a Product, (a) Isis will have the first right, but not the obligation, to defend against any such Proceeding initiated prior to Option exercise at its sole cost and expense and (b) Roche will have the first right, but not the obligation, to defend against any such Proceeding initiated after Option exercise at its sole cost and expense. If the Party having the first right to defend against such Proceeding (the "***Lead Party***") elects to defend against such Proceeding, then the Lead Party will have the sole right to direct the defense and to elect whether to settle such claim (but only with the prior written consent of the other Party, not to be unreasonably withheld, conditioned or delayed). The other Party will reasonably assist the Lead Party in defending such Proceeding and cooperate in any such litigation at the request and expense of the Lead Party. The Lead Party will provide the other Party with prompt written notice of the commencement of any such Proceeding that is of the type described in this Section 7.4, and the Lead Party will keep the other Party apprised of the progress of such Proceeding. If the Lead Party elects not to defend against a Proceeding, then the Lead Party will so notify the other Party in writing within sixty (60) days after the Lead Party first receives written notice of the initiation of such Proceeding, and the other Party (the "***Step-In Party***") will have the right, but not the obligation, to defend against such Proceeding at its sole cost and expense and thereafter the Step-In Party will have the sole right to direct the defense thereof, including the right to settle such claim. In any event, the Party not defending such Proceeding will reasonably assist the other Party and cooperate in any such litigation at the request and expense of the Party defending such Proceeding. Each Party may at its own expense and with its own counsel join any defense initiated or directed by the other Party under this Section 7.4. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding under this Section 7.4, and such Party will promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party.

7.4.2. **Discontinued Product**. If a Third Party initiates a Proceeding claiming that any Patent Right or Know-How owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of a Discontinued Product, Isis will have the first right, but not the obligation, to defend against and settle such Proceeding at its sole cost and expense. Roche will reasonably assist Isis in defending such Proceeding and cooperate in any such litigation at the request and expense of Isis. Each Party may at its own expense and with its own counsel join any defense directed by the other Party. Isis will provide Roche with prompt written notice of the commencement of any such Proceeding, or of any allegation of infringement of which Isis becomes aware and that is of the type described in this Section 7.4.2, and Isis will promptly furnish Roche with a copy of each communication relating to the alleged infringement received by Isis.

7.4.3. **Interplay Between Enforcement of IP and Defense of Third Party Claims**. Notwithstanding the provisions of Section 7.4.1 and Section 7.4.2, to the extent that a Party's defense against a Third Party claim of infringement under this Section 7.4 involves (i) the enforcement of the other Party's Know-How or Patent Rights, or (ii) the defense of an invalidity claim with respect to such other Party's Know-How or Patent Rights, then, in each case, the general concepts of Section 7.5 will apply to the enforcement of such other Party's Know-How or Patent Rights or the defense of such invalidity claim (i.e., each Party has the right to enforce its own intellectual property, except that the relevant Commercializing Party will have the initial right, to the extent provided in Section 7.5, to enforce such Know-How or Patent Rights or defend such invalidity claim, and the other Party will have a step-in right, to the extent provided in Section 7.5, to enforce such Know-How or Patent Rights or defend such invalidity claim).

7.5. **Enforcement of Patents Against Competitive Infringement**.

7.5.1. **Duty to Notify of Competitive Infringement**. If either Party learns of an infringement, unauthorized use, misappropriation or threatened infringement by a Third Party to which such Party does not owe any obligation of confidentiality with respect to any Product-Specific Patents by reason of the development, manufacture, use or commercialization of a product directed against the RNA that encodes HTT in the Field ("***Competitive Infringement***"), such Party will promptly notify the other Party in writing and will provide such other Party with available evidence of such Competitive Infringement; *provided*, *however*, that for cases of Competitive Infringement under Section 7.5.7 below, such written notice will be given within ten (10) Business Days.

7.5.2. **Prior to Option Exercise**. For any Competitive Infringement occurring after the Effective Date but before Option exercise, Isis will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto, by counsel of its own choice, and Roche will have the right to be represented in that action by counsel of its own choice at its own expense, *however*, Isis will have the sole right to control such litigation. Isis will provide Roche with prompt written notice of the commencement of any such Proceeding, and Isis will keep Roche apprised of the progress of such Proceeding. If Isis fails to initiate a Proceeding within a period of ninety (90) days after receipt of written notice of such Competitive Infringement (subject to a ninety (90) day extension to conclude negotiations, which extension will apply only in the event that Isis has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such ninety (90) day period), Roche will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice; *provided that* Isis will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, Isis will at all times have the sole right to institute, prosecute, and control any Proceeding under this Section 7.5.2 to the extent involving any Isis Core Technology Patents or Isis Manufacturing and Analytical Patents.

7.5.3. **Following Option Exercise**. For any Competitive Infringement with respect to a Product (except for a Discontinued Product) occurring after Option exercise, so long as part of such Proceeding Roche also enforces any Patent Rights Controlled by Roche being infringed that Cover a Product, then Roche will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto by counsel of its own choice at its own expense, and Isis will have the right, at its own expense, to be represented in that action by counsel of its own choice, *however,* Roche will have the right to control such litigation. If Roche fails to initiate a Proceeding within a period of ninety (90) days after receipt of written notice of such Competitive Infringement (subject to a ninety (90) day extension to conclude negotiations, if Roche has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such ninety (90) day period), Isis will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice, and Roche will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, Isis will at all times have the sole right to institute, prosecute, and control any Proceeding under this Section 7.5.3 to the extent involving any Isis Core Technology Patents or Isis Manufacturing and Analytical Patents.

7.5.4. **Joinder**.

(a) If a Party initiates a Proceeding in accordance with this Section 7.5, the other Party agrees to be joined as a party plaintiff where necessary and to give the first Party reasonable assistance and authority to file and prosecute the Proceeding. Subject to Section 7.5.5, the costs and expenses of each Party incurred pursuant to this Section 7.5.4(a) will be borne by the Party initiating such Proceeding.

(b) If one Party initiates a Proceeding in accordance with this Section 7.5.4, the other Party may join such Proceeding as a party plaintiff where necessary for such other Party to seek lost profits with respect to such infringement.

7.5.5. **Share of Recoveries**. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 7.5 will be shared as follows:

(a) the amount of such recovery will first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts will be allocated *pro rata* if insufficient to cover the totality of such expenses); then

(b) any remaining proceeds constituting direct or actual damages for acts of infringement occurring prior to Roche's exercise of the Option will be (i) [***]; or (ii) [***]; then

(c) any remaining proceeds constituting direct or actual damages for acts of infringement occurring after Roche's exercise of the Option will be treated [***], and [***]; then

(d) any remaining proceeds constituting punitive or treble damages will be allocated between the Parties as follows: the Party initiating the Proceeding will receive and retain [***] of such proceeds and the other Party will receive and retain [***] of such proceeds.

7.5.6. **Settlement**. Notwithstanding anything to the contrary under this ARTICLE 7, neither Party may enter a settlement, consent judgment or other voluntary final disposition of a suit under this ARTICLE 7 that disclaims, limits the scope of, admits the invalidity or unenforceability of, or grants a license, covenant not to sue or similar immunity under a Patent Right Controlled by the other Party without first obtaining the written consent of the Party that Controls the relevant Patent Right.

7.5.7. **35 USC 271(e)(2) Infringement**. Notwithstanding anything to the contrary in this Section 7.5, solely with respect to Licensed Patents, for a Competitive Infringement under 35 USC 271(e)(2), the time period set forth in Section 7.5.2 during which a Party will have the initial right to bring a Proceeding will be shortened to a total of twenty-five (25) days, so that, to the extent the other Party has the right, pursuant to such Section to initiate a Proceeding if the first Party does not initiate a Proceeding, such other Party will have such right if the first Party does not initiate a Proceeding within twenty-five (25) days after such first Party's receipt of written notice of such Competitive Infringement.

7.6. Other Infringement.

7.6.1. Jointly-Owned Collaboration Patents. With respect to the infringement of a Jointly-Owned Collaboration Patent which is not a Competitive Infringement, the Parties will cooperate in good faith to bring suit together against such infringing party or the Parties may decide to permit one Party to solely bring suit. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 7.6.1 will be shared as follows: (i) the amount of such recovery will first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts will be allocated *pro rata* if insufficient to cover the totality of such expenses); (ii) any remaining proceeds constituting direct damages will be [***], and (iii) any remaining proceeds constituting punitive or treble damages will be allocated as follows: (A) if the Parties jointly initiate a Proceeding pursuant to this Section 7.6.1, [***] of such proceeds; and (B) if only one Party initiates the Proceeding pursuant to this Section 7.6.1, such Party will receive [***] of such proceeds and the other Party will receive [***] of such proceeds.

7.6.2. Patents Solely Owned by Isis. Isis will retain all rights to pursue an infringement of any Patent Right solely owned by Isis which is other than a Competitive Infringement and Isis will retain all recoveries with respect thereto.

7.6.3. Patents Solely Owned by Roche. Roche will retain all rights to pursue an infringement of any Patent Right solely owned by Roche which is other than a Competitive Infringement and Roche will retain all recoveries with respect thereto.

7.7. Patent Listing.

7.7.1. Roche's Obligations. Roche will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover a Product. Prior to such listings, the Parties will meet, through the Joint Patent Committee, to evaluate and identify all applicable Patent Rights, and Roche will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Committee for any such listing. Notwithstanding the preceding sentence, Roche will retain final decision-making authority as to the listing of all applicable Patent Rights for a Product that are not Isis Core Technology Patents or Isis Manufacturing and Analytical Patents, regardless of which Party owns such Patent Rights.

7.7.2. **Isis' Obligations**. Isis will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover a Discontinued Product. Prior to such listings, the Parties will meet, through the Joint Patent Committee, to evaluate and identify all applicable Patent Rights, and Isis will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Committee for any such listing. Notwithstanding the preceding sentence, Isis will retain final decision-making authority as to the listing of all applicable Patent Rights for such Discontinued Products, as applicable, regardless of which Party owns such Patent Rights.

7.8. **CREATE Act**. Notwithstanding anything to the contrary in this ARTICLE 7, neither Party will have the right to make an election under the CREATE Act when exercising its rights under this ARTICLE 7 without the prior written consent of the other Party, which will not be unreasonably withheld, conditioned or delayed. With respect to any such permitted election, the Parties will use reasonable efforts to cooperate and coordinate their activities with respect to any submissions, filings or other activities in support thereof. The Parties acknowledge and agree that this Agreement is a "*joint research agreement*" as defined in the CREATE Act.

7.9. **Obligations to Third Parties**. Notwithstanding any of the foregoing, each Party's rights and obligations with respect to Licensed Technology under this ARTICLE 7 will be subject to the Third Party rights and obligations under any (i) Third Party agreements the restrictions and obligations of which Roche has agreed to under Section 6.11.2(b), (ii) Prior Agreements, and (iii) Isis In-License Agreements; *provided*, *however*, that, to the extent that Isis has a non-transferable right to prosecute, maintain or enforce any Patent Rights licensed to Roche hereunder and, this Agreement purports to grant any such rights to Roche, Isis will act in such regard with respect to such Patent Rights at Roche's direction.

7.10. **Additional Right and Exceptions**. Notwithstanding any provision of this ARTICLE 7, but subject to Section 7.4.3, Isis retains the sole right to Prosecute and Maintain Isis Core Technology Patents and Isis Manufacturing and Analytical Patents during the Agreement Term and to control any enforcement of Isis Core Technology Patents and Isis Manufacturing and Analytical Patents, and will take the lead on such enforcement solely to the extent that the scope or validity of any Patent Rights Controlled by Isis and Covering the Isis Core Technology Patents or Isis Manufacturing and Analytical Patents is at risk. If Isis determines, in Isis' sole discretion, to not enforce any Isis Core Technology Patents or Isis Manufacturing and Analytical Patents and does not permit Roche to so enforce such Patent Rights, then the Parties will mutually agree on an appropriate adjustment (if any) of the future consideration payable by Roche under this Agreement to reflect any adverse impact Isis' failure to enforce such Patent Rights has on Products.

7.11. **Patent Term Extension**. The Parties will cooperate with each other in gaining patent term extension wherever applicable to a Product, including European supplementary protection certificates and pediatric exclusivity. After exercising the Option, Roche will determine which patents will be extended and what extensions will be sought.

7.12. **No Challenge**. If, during the Agreement Term, solely with respect to rights to the Licensed Patents that are included (or, prior to Option exercise, are eligible to be included) in a license granted to Roche under Section 4.1.1, Roche, its Affiliates or Sublicensees, in the United States or any other country, (a) commence or otherwise voluntarily determine to participate in (other than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) any action or proceeding, challenging or denying the enforceability or validity of any claim within an issued patent or patent application within such Licensed Patents, or (b) direct, support or actively assist any other Person (other than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) in bringing or prosecuting any action or proceeding challenging or denying the validity of any claim within an issued patent or patent application within such Licensed Patents, then unless, within thirty (30) days after written notice from Isis, Roche rescinds any actions brought by Roche, its Affiliates, or Sublicensees, Isis may terminate this Agreement and the provisions of Section 10.4.1 and Section 10.4.2 will apply; [***].

ARTICLE 8.
REPRESENTATIONS AND WARRANTIES

8.1. **Representations and Warranties of Both Parties**. Each Party hereby represents and warrants to the other Party, as of the Effective Date, that:

8.1.1. such Party is duly organized, validly existing and in good standing under the laws of the jurisdiction of its incorporation or organization and has full corporate power and authority to enter into this Agreement and to carry out the provisions hereof;

8.1.2. such Party has taken all necessary action on its part to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder;

8.1.3. this Agreement has been duly executed and delivered on behalf of such Party, and constitutes a legal, valid and binding obligation, enforceable against it in accordance with the terms hereof;

8.1.4. the execution, delivery and performance of this Agreement by such Party will not constitute a default under or conflict with any agreement, instrument or understanding, oral or written, to which it is a party or by which it is bound, or to the best of its knowledge and belief violate any law or regulation of any court, governmental body or administrative or other agency having jurisdiction over such Party;

8.1.5. to the best of its knowledge and belief, no government authorization, consent, approval, license, exemption of or filing or registration with any court or governmental department, commission, board, bureau, agency or instrumentality, domestic or foreign, under any applicable laws, rules or regulations currently in effect, is or will be necessary for, or in connection with, the transaction contemplated by this Agreement or any other agreement or instrument executed in connection herewith, or for the performance by it of its obligations under this Agreement and such other agreements; and

8.1.6. it has not employed (and, to the best of its knowledge and belief, has not used a contractor or consultant that has employed) and in the future will not employ (or, to the best of its knowledge, use any contractor or consultant that employs, provided that such Party may reasonably rely on a representation made by such contractor or consultant) any Person debarred by the FDA (or subject to a similar sanction of EMA or foreign equivalent), or any Person which is the subject of an FDA debarment investigation or proceeding (or similar proceeding of EMA or foreign equivalent), in the conduct of the Pre-Clinical Studies or Clinical Studies of a Product and its activities under the R&D Plans.

8.2. **Representations and Warranties of Isis**. Isis hereby represents and warrants to Roche, as of the Effective Date, that:

8.2.1. To the best of its knowledge and belief, there are no additional licenses (beyond those that would be granted to Roche under Section 4.1.1 upon the exercise of the Option for a Product arising under the Isis Development Candidate-R&D Plan) under any intellectual property owned or Controlled by Isis or its Affiliates as of the Effective Date that would be required in order for Roche to further Develop and Commercialize a Product arising under the Isis Development Candidate-R&D Plan existing on the Effective Date.

8.2.2. The Licensed Technology existing as of the Effective Date constitutes all of the Patent Rights and Know-How Controlled by Isis as of the Effective Date that are necessary to Develop, Manufacture or Commercialize Compounds contemplated under the Isis Development Candidate-R&D Plan existing on the Effective Date in the Field. Isis has not previously assigned, transferred, conveyed or otherwise encumbered its right, title and interest in the Licensed Technology in a manner that conflicts with any rights granted to Roche hereunder.

8.2.3. There are no claims, judgments or settlements against or owed by Isis or its Affiliates or pending against Isis or, to the best of Isis' knowledge, threatened against Isis, in each case relating to the Isis Technology that could impact activities under this Agreement. To the best of Isis' knowledge, there are no claims, judgments or settlements against or owed by any Third Party that is party to a Prior Agreement, or pending or threatened claims or litigation against any Third Party that is party to a Prior Agreement, in each case relating to the Isis Technology that would impact activities under this Agreement.

8.2.4. SCHEDULE 8.2.4(a), SCHEDULE 8.2.4(b) and SCHEDULE 8.2.4(c) set forth true, correct and complete lists of all Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, and Isis Product-Specific Patents that apply to the Compounds contemplated under the Isis Development Candidate-R&D Plan as of the Effective Date, respectively, and indicates whether each such Patent Right is owned by Isis or licensed by Isis from a Third Party and if so, identifies the licensor or sublicensor from which the Patent Right is licensed. Isis Controls such Patent Rights existing as of the Effective Date and is entitled to grant all rights and licenses (or sublicenses, as the case may be) under such Patent Rights it purports to grant to Roche under this Agreement.

8.2.5. (a) There is no fact or circumstance known by Isis that would cause Isis to reasonably conclude that any Licensed Patent is invalid or un-enforceable, (b) there is no fact or circumstance known by Isis that would cause Isis to reasonably conclude the inventorship of each Licensed Patent is not properly identified on each patent, (c) all official fees, maintenance fees and annuities for the Licensed Patents have been paid and all administrative procedures with governmental agencies have been completed, (d) none of the Isis Product-Specific Patents that would be licensed by Isis to Roche upon Option exercise under this Agreement are currently involved in any interference, reissue, re-examination, cancellation or opposition proceeding and neither Isis, nor any of its Affiliates, has received any written notice from any person, or has knowledge, of such actual or threatened proceeding, and (e) to the best of Isis' knowledge and belief, Roche's practice of the inventions claimed in the Isis Product-Specific Patents in the performance of the Roche R&D Activities contemplated as of the Effective Date will not [***].

8.2.6. SCHEDULE 6.11.1 sets forth true, correct and complete lists of all Isis In-License Agreements relating to Licensed Technology necessary or useful to conduct the research, Development, Manufacture or Commercialization of Compounds as contemplated under the Isis Development Candidate-R&D Plan existing on the Effective Date. All Isis In-License Agreements are in full force and effect and have not been modified or amended. Neither Isis nor, to the best knowledge of Isis, the Third Party licensor in an Isis In-License Agreement is in default with respect to a material obligation under such Isis In-License Agreement, and neither such party has claimed or has grounds upon which to claim that the other party is in default with respect to a material obligation under, any Isis In-License Agreement.

8.2.7. SCHEDULE 8.2.7 is a complete and accurate list of all agreements that create Third Party Obligations that affect the rights granted by Isis to Roche under this Agreement with respect to Isis Development Candidates contemplated by the R&D Plans on the Effective Date.

8.2.8. Isis has all rights necessary to grant the option and licenses contained in this Agreement, and has the ability to work exclusively with Roche as set forth in this Agreement, including the covenants granted in Section 2.1.

8.3. **Isis Covenants**. Isis hereby covenants to Roche that, except as expressly permitted under this Agreement:

8.3.1. Isis will promptly amend Schedule 8.2.4(a), Schedule 8.2.4(b) and Schedule 8.2.4(c) and submit such amended Schedules to Roche if Isis becomes aware that any Isis Core Technology Patents, Isis Manufacturing and Analytical Patents or Isis Product-Specific Patents are not properly identified on such Schedule.

8.3.2. during the Agreement Term, Isis will maintain and not breach any Isis In-License Agreements and any agreements with Third Parties entered into after the Effective Date ("***New Third Party Licenses***") that provide a grant of rights from such Third Party to Isis that are Controlled by Isis and are licensed or may become subject to a license from Isis to Roche for a Product under this Agreement;

8.3.3. Isis will promptly notify Roche of any material breach by Isis or a Third Party of any New Third Party License, and in the event of a breach by Isis, will permit Roche to cure such breach on Isis' behalf upon Roche's request;

8.3.4. Isis will not amend, modify or terminate any Isis In-License Agreement or New Third Party License in a manner that would adversely affect Roche's rights hereunder without first obtaining Roche's written consent, which consent may be withheld in Roche's sole discretion;

8.3.5. Isis will not enter into any new agreement or other obligation with any Third Party, or amend an existing agreement with a Third Party, in each case that restricts, limits or encumbers the rights granted to Roche under this Agreement;

8.3.6. Isis will cause its Affiliates, licensees and sublicensees to comply with the terms of Section 2.1;

8.3.7. all employees and contractors of Isis performing Development activities hereunder on behalf of Isis will be obligated to assign all right, title and interest in and to any inventions (or grant a license to Isis or an option to obtain such a license) developed by them, whether or not patentable, to Isis or such Affiliate, respectively, as the sole owner thereof; and

8.3.8. If, after the Effective Date, Isis becomes the owner or otherwise acquires Control of any formulation or delivery technology that would be necessary or useful in order for Roche to further Develop, Manufacture or Commercialize a Product, and Roche has exercised its Option and the license granted to Roche under this Agreement is in effect, Isis will make such technology available to Roche on commercially reasonable terms.

8.4. **Representations and Warranties of Roche**. Roche hereby represents and warrants to Isis, as of the Effective Date, that:

8.4.1. SCHEDULE 8.4.1 sets forth a true and correct list of Patent Rights owned or Controlled as of the Effective Date by Roche or its Affiliates that (i) specifically claim Roche's Brain Shuttle technology, or (ii) are necessary or useful for the research, Development or Commercialization of a Brain Shuttle Development Candidate (such Patent Rights, "***Roche Existing Brain Shuttle Patents***"). Roche Controls such Roche Existing Brain Shuttle Patents existing as of the Effective Date and is entitled to grant all rights and licenses (or sublicenses, as the case may be) under such Roche Existing Brain Shuttle Patents it purports to grant to Isis under this Agreement; and

8.4.2. (a) There is no fact or circumstance known by Roche that would cause Roche to reasonably conclude that any Roche Existing Brain Shuttle Patent is invalid or un-enforceable, (b) there is no fact or circumstance known by Roche that would cause Roche to reasonably conclude the inventorship of each Roche Existing Brain Shuttle Patent is not properly identified on each patent, (c) all official fees, maintenance fees and annuities for the Roche Existing Brain Shuttle Patents have been paid and all administrative procedures with governmental agencies have been completed, (d) none of the Roche Existing Brain Shuttle Patent are currently involved in any interference, reissue, re-examination, cancellation or opposition proceeding and neither Isis, nor any of its Affiliates, has received any written notice from any person, or has knowledge, of such actual or threatened proceeding, and (e) to the best of Roche's knowledge and belief, Isis' practice of the inventions claimed in the Roche Existing Brain Shuttle Patents in the performance of the Isis R&D Activities contemplated as of the Effective Date will not infringe the Patent Rights of any Third Party.

8.5. **DISCLAIMER. EXCEPT AS OTHERWISE EXPRESSLY SET FORTH IN THIS AGREEMENT, NEITHER PARTY NOR ITS AFFILIATES MAKES ANY REPRESENTATION OR EXTENDS ANY WARRANTY OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. ROCHE AND ISIS UNDERSTAND THAT PRODUCTS ARE THE SUBJECT OF ONGOING RESEARCH AND DEVELOPMENT AND THAT NEITHER PARTY CAN ASSURE THE SAFETY, USEFULNESS OR COMMERCIAL OR TECHNICAL VIABILITY OF THE PRODUCTS.**

ARTICLE 9.
INDEMNIFICATION; INSURANCE

9.1. **Indemnification by Roche**. Roche will indemnify, defend and hold harmless Isis and its Affiliates, and its or their respective directors, officers, employees and agents, from and against any and all liabilities, damages, losses, costs and expenses including the reasonable fees of attorneys (collectively "***Losses***") arising out of or resulting from any and all Third Party suits, claims, actions, proceedings or demands ("***Claims***") based upon:

9.1.1. the gross negligence or willful misconduct of Roche, its Affiliates or Sublicensees and its or their respective directors, officers, employees and agents, in connection with Roche's performance of its obligations or exercise of its rights under this Agreement;

9.1.2. any breach of any representation or warranty or express covenant made by Roche under ARTICLE 8 or any other provision under this Agreement;

9.1.3. the Development or Manufacturing activities that are conducted by or on behalf of Roche or its Affiliates or Sublicensees (which will exclude any Development or Manufacturing activities that are conducted by or on behalf of Isis pursuant to this Agreement); or

9.1.4. the Commercialization of a Product by or on behalf of Roche or its Affiliates or Sublicensees;

except, in each case above, to the extent such Claim arose out of or resulted from or is attributable to any acts or omissions of Isis or its Affiliates, licensees, Sublicensees or contractors, and its or their respective directors, officers, employees and agents or other circumstance for which Isis has an indemnity obligation pursuant to Section 9.2.

9.2. **Indemnification by Isis**. Isis will indemnify, defend and hold harmless Roche and its Affiliates, and its or their respective directors, officers, employees and agents, from and against any and all Losses arising out of or resulting from any and all Claims based upon:

9.2.1. the gross negligence or willful misconduct of Isis, its Affiliates or Sublicensees or its or their respective directors, officers, employees and agents, in connection with Isis' performance of its obligations or exercise of its rights under this Agreement;

9.2.2. any breach of any representation or warranty or express covenant made by Isis under ARTICLE 8 or any other provision under this Agreement;

9.2.3. any Development or Manufacturing activities that are conducted by or on behalf of Isis or its Affiliates or Sublicensees (which will exclude any Development or Manufacturing activities that are conducted by or on behalf of Roche pursuant to this Agreement); or

9.2.4. any development, manufacturing or commercialization activities that are conducted by or on behalf of Isis or its Affiliates or Sublicensees with respect to a Discontinued Product.

except, in each case above, to the extent such Claim arose out of or resulted from or is attributable to any acts or omissions of Roche or its Affiliates, licensees, Sublicensees or contractors and its or their respective directors, officers, employees and agents or other circumstance for which Roche has an indemnity obligation pursuant to Section 9.1.

9.3. **Procedure**. If a Person entitled to indemnification under Section 9.1 or Section 9.2 (an "***Indemnitee***") seeks such indemnification, such Indemnitee will (i) inform the indemnifying Party in writing of a Claim as soon as reasonably practicable after such Indemnitee receives notice of such Claim, (ii) permit the indemnifying Party to assume direction and control of the defense of the Claim (including the sole right to settle such Claim at the sole discretion of the indemnifying Party, *provided that* such settlement or compromise does not admit any fault or negligence on the part of the Indemnitee, or impose any obligation on, or otherwise materially adversely affect, the Indemnitee or other Party), (iii) cooperate as reasonably requested (at the expense of the indemnifying Party) in the defense of the Claim, and (iv) undertake reasonable steps to mitigate any Losses with respect to the Claim. The provisions of Section 7.4 will govern the procedures for responding to a Claim of infringement described therein. Notwithstanding anything in this Agreement to the contrary, the indemnifying Party will have no liability under Section 9.1 or Section 9.2, as the case may be, for Claims settled or compromised by the Indemnitee without the indemnifying Party's prior written consent.

9.4. **Insurance**.

9.4.1. **Isis' Insurance Obligations**. Isis will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement, including but not limited to its indemnification obligations herein, in such amounts and on such terms as are customary for prudent practices for biotech companies of similar size and with similar resources in the pharmaceutical industry for the activities to be conducted by it under this Agreement taking into account the scope of development of products. Isis will furnish to Roche evidence of any insurance required under this Section 9.4.1, upon request.

9.4.2. **Roche's Insurance Obligations**. Roche hereby represents and warrants to Isis that it will maintain, at its cost, reasonable insurance or self insure against liability and other risks associated with its activities contemplated by this Agreement (including product liability), including but not limited to its indemnification obligations herein, in such amounts and on such terms as are customary for prudent practices for large companies in the pharmaceutical industry for the activities to be conducted by Roche under this Agreement. Roche will maintain such self insurance throughout the Agreement Term and for five years thereafter, and will furnish to Isis evidence of such insurance, upon request.

9.5. **LIMITATION OF CONSEQUENTIAL DAMAGES**. **EXCEPT FOR (a) CLAIMS OF A THIRD PARTY THAT ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 9, (b) CLAIMS ARISING OUT OF A PARTY'S WILLFUL MISCONDUCT OF THIS AGREEMENT, (c) A PARTY'S BREACH OF ARTICLE 2, OR A BREACH OF SECTION 10.4.1(b) BY ROCHE OR ITS AFFILIATES OR (d) CLAIMS ARISING OUT OF A PARTY'S BREACH OF ITS CONFIDENTIALITY OBLIGATIONS UNDER THIS AGREEMENT, NEITHER PARTY NOR ANY OF ITS AFFILIATES WILL BE LIABLE TO THE OTHER PARTY TO THIS AGREEMENT OR ITS AFFILIATES FOR ANY INCIDENTAL, CONSEQUENTIAL, SPECIAL, PUNITIVE OR OTHER INDIRECT DAMAGES, WHETHER LIABILITY IS ASSERTED IN CONTRACT, TORT (INCLUDING NEGLIGENCE AND STRICT PRODUCT LIABILITY), INDEMNITY OR CONTRIBUTION, AND IRRESPECTIVE OF WHETHER THAT PARTY OR ANY REPRESENTATIVE OF THAT PARTY HAS BEEN ADVISED OF, OR OTHERWISE MIGHT HAVE ANTICIPATED THE POSSIBILITY OF, ANY SUCH LOSS OR DAMAGE.**

ARTICLE 10.
TERM; TERMINATION

10.1. **Agreement Term; Expiration**. This Agreement is effective as of the Effective Date and, unless earlier terminated pursuant to the other provisions of this ARTICLE 10, will continue in full force and effect until this Agreement expires as follows:

10.1.1. on a country-by-country basis, on the date of expiration of all payment obligations by the Commercializing Party under this Agreement with respect to a Product (or a Discontinued Product) in such country;

10.1.2. in its entirety upon the expiration of all payment obligations under this Agreement with respect to the last Product (or last Discontinued Product) in all countries pursuant to Section 10.1.1; and

10.1.3. where Roche has not provided Isis a written notice stating Roche is exercising its Option under Section 6.3 by the Option Deadline.

The period from the Effective Date until the date of expiration of this Agreement pursuant to this Section 10.1 is the "***Agreement Term***." On a Product-by-Product basis, if with respect to a particular Product this Agreement expires (i.e., is not terminated early) under Section 10.1.1 or Section 10.1.2 in a particular country, then, effective upon such expiration, Isis will and hereby does grant to Roche a fully paid-up and irrevocable non-exclusive license under the Licensed Technology to Manufacture, Develop and Commercialize the Product that is the subject of such expiration in such country.

10.2. **Termination of the Agreement**.

10.2.1. **Roche's Termination for Convenience**. After payment by Roche of the upfront fee under Section 6.1, subject to Section 10.4.1 below, Roche may terminate this Agreement for convenience by providing ninety (90) days written notice to Isis of such termination. If Roche terminates this Agreement for convenience under this Section 10.2.1 prior to Roche paying Isis the milestone payment for achievement of the Initiation of a Phase 1 Trial Milestone Event, then if (i) Isis continues to develop the Product after such termination and achieves the Initiation of the Phase 1 Trial Milestone Event for such Product, and (ii) Isis has not granted a Third Party an exclusive license or an exclusive option to obtain an exclusive license to such Product by the [***], then [***], unless by that time Isis has undergone or has agreed to a Change of Control, in which case no such payment shall be due or payable.

10.2.2. Termination for Material Breach.

(a) **Roche's Right to Terminate**. If Roche believes that Isis is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under ARTICLE 1, which is governed by Section 10.2.3 below), then Roche may deliver notice of such material breach to Isis. If the breach is curable, Isis will have sixty (60) days to cure such breach. If Isis fails to cure such breach within the sixty (60) day period, or if the breach is not subject to cure, Roche may terminate this Agreement by providing written notice to Isis.

(b) **Isis' Right to Terminate**. If Isis believes that Roche is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under ARTICLE 1 or Section 5.1, which is governed by Section 10.2.3 below), then Isis may deliver notice of such material breach to Roche. If the breach is curable, Roche will have sixty (60) days to cure such breach (except to the extent such breach involves the failure to make a payment when due, which breach must be cured within thirty (30) days following such notice). If Roche fails to cure such breach within the sixty (60) day or thirty (30) day period, as applicable, or if the breach is not subject to cure, Isis may terminate this Agreement by providing written notice to Roche.

10.2.3. Remedies for Failure to Use Commercially Reasonable Efforts.

(a) If Isis, in Roche's reasonable determination, fails to use Commercially Reasonable Efforts in the activities contemplated in ARTICLE 1 prior to Option exercise, Roche will notify Isis and, within thirty (30) days thereafter, Isis and Roche will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to Isis' use of Commercially Reasonable Efforts in ARTICLE 1. Following such a meeting, if Isis fails to use Commercially Reasonable Efforts as contemplated by ARTICLE 1, then subject to Section 10.2.4 below, Roche will have the right, at its sole discretion, to (i) terminate this Agreement, or (ii) prior to Option exercise, Roche may elect to trigger the alternative remedy provisions of Section 10.3 below in lieu of terminating this Agreement by providing written notice to Isis. If Roche elects to trigger the alternative remedy provisions of Section 10.3 below, then such election is Roche's sole and exclusive remedy if Isis fails to use Commercially Reasonable Efforts in the activities contemplated in ARTICLE 1 prior to Option exercise.

(b) If Roche, in Isis' reasonable determination, fails to use Commercially Reasonable Efforts under ARTICLE 1 or Section 5.1 above, Isis will notify Roche and, within thirty (30) days thereafter, Isis and Roche will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to Roche's use of Commercially Reasonable Efforts in ARTICLE 1 or Section 5.1. Following such a meeting, if Roche fails to use Commercially Reasonable Efforts as contemplated by ARTICLE 1 or Section 5.1, then subject to Section 10.2.4 below, Isis will have the right, at its sole discretion, to terminate this Agreement.

10.2.4. **Disputes Regarding Material Breach**. Notwithstanding the foregoing, if the Breaching Party in Section 10.2.2 or Section 10.2.3 disputes in good faith the existence, materiality, or failure to cure of any such breach which is not a payment breach, and provides notice to the Non-Breaching Party of such dispute within such sixty (60) day period, the Non-Breaching Party will not have the right to terminate this Agreement in accordance with Section 10.2.2 or Section 10.2.3, or trigger the alternative remedy provisions of Section 10.3, as applicable, unless and until it has been determined in accordance with Section 12.1 that this Agreement was materially breached by the Breaching Party and the Breaching Party fails to cure such breach within thirty (30) days following such determination. It is understood and acknowledged that during the pendency of such dispute, all the terms of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder, including satisfying any payment obligations.

10.2.5. **Termination for Insolvency**.

(a) Either Party may terminate this Agreement if, at any time, the other Party files in any court or agency pursuant to any statute or regulation of any state or country a petition in bankruptcy or insolvency or for reorganization or for an arrangement or for the appointment of a receiver or trustee of the Party or of substantially all of its assets; or if the other Party proposes a written agreement of composition or extension of substantially all of its debts; or if the other Party will be served with an involuntary petition against it, filed in any insolvency proceeding, and such petition will not be dismissed within ninety (90) days after the filing thereof; or if the other Party will propose or be a party to any dissolution or liquidation; or if the other Party will make an assignment of substantially all of its assets for the benefit of creditors.

(b) All rights and licenses granted under or pursuant to any section of this Agreement are and will otherwise be deemed to be for purposes of Section 365(n) of Title 11, United States Code (the "***Bankruptcy Code***") licenses of rights to "intellectual property" as defined in Section 101(56) of the Bankruptcy Code. The Parties will retain and may fully exercise all of their respective rights and elections under the Bankruptcy Code. Upon the bankruptcy of any Party, the non-bankrupt Party will further be entitled to a complete duplicate of, or complete access to, any such intellectual property, and such, if not already in its possession, will be promptly delivered to the non-bankrupt Party, unless the bankrupt Party elects in writing to continue, and continues, to perform all of its obligations under this Agreement.

10.2.6. Termination if Development Candidate Not Identified.

(a) ***Failure to Identify a Brain Shuttle Development Candidate***. If, despite the Parties' Commercially Reasonable Efforts, Roche has not designated at least one Brain Shuttle Development Candidate by the [***] of the Effective Date, then either Party will have the right to terminate this Agreement solely with respect to the Brain Shuttle Development Candidate-R&D Plan by providing written notice to the other Party within [***] of the Effective Date. In the case of termination of this Agreement under this Section 10.2.6(a), Section 10.4.1 will apply solely with respect to the Brain Shuttle Development Candidate-R&D Plan. Nothing in this Section 10.2.6(a) will terminate or otherwise affect the provisions of this Agreement with respect to the Isis Development Candidate-R&D Plan, which shall remain in full force and effect.

(b) ***Failure to Identify an Isis Development Candidate***. If, despite Isis' Commercially Reasonable Efforts, Isis has not designated at least one Isis Development Candidate by the [***] of the Effective Date, then either Party will have the right to terminate this Agreement with respect to the Isis Development Candidate-R&D Plan by providing written notice to the other Party within [***] of the Effective Date. In the case of termination of this Agreement under this Section 10.2.6(b), Section 10.4.1 will apply solely with respect to the Isis Development Candidate-R&D Plan. Nothing in this Section 10.2.6(b) will terminate or otherwise affect the provisions of this Agreement with respect to the Brain Shuttle Development Candidate-R&D Plan, which shall remain in full force and effect.

10.3. Alternative Remedies to Termination Available to Roche Prior to Option Exercise. If, prior to Option exercise, Roche elects to exercise the alternative remedy provisions of this Section 10.3 in lieu of terminating this Agreement by providing written notice of such election to Isis in accordance with Section 10.2.3(a), then this Agreement will continue in full force and effect with the following modifications:

(a) Isis will have no further obligations under the R&D Plans, and Roche is responsible for the continued research, Development and Commercialization of Products (including meeting all remaining performance obligations under ARTICLE 1 and Section 5.1);

(b) effective as of the date of Roche's notice to Isis electing the alternative remedy provisions of this Section 10.3, Roche will be deemed for all purposes of this Agreement to have exercised the Option;

(c) Roche will have and Isis grants, the exclusive license under Section 4.1.1;

(d) Isis will perform its obligations under Section 4.2 within sixty (60) days of Roche electing to exercise its alternative remedies under this Section 10.3; and

(e) the financial provisions of ARTICLE 6 will be modified as follows:

(i) [***] *Payments*. Roche will [***]; and

(ii) *License Fee*. The license fee set forth in Section 6.3 will be [***]. Such [***] will be due within [***] after the [***] but in no event later than [***].

The milestone provisions of Section 6.4 and Section 6.5 and the royalty provisions of Section 6.7 will [***].

10.4. Consequences of Expiration or Termination of the Agreement.

10.4.1. In General. If this Agreement expires or is terminated by a Party in accordance with this ARTICLE 10 at any time and for any reason, the following terms will apply to any such expiration or termination:

(a) **Return of Information and Materials**. The Parties will return (or destroy, as directed by the other Party) all data, files, records and other materials containing or comprising the other Party's Confidential Information that are the subject of such termination. Notwithstanding the foregoing, the Parties will be permitted to retain one copy of such data, files, records, and other materials for archival and legal compliance purposes.

(b) **License Termination**. Except for the licenses granted under Section 4.1.2, any licenses granted by Isis to Roche under this Agreement will terminate and Roche, its Affiliates and Sublicensees will cease selling all Products.

(c) **Exclusivity Covenants**. Neither Party will have any further obligations under Section 2.1.1 of this Agreement.

(d) **Accrued Rights**. Termination or expiration of this Agreement for any reason will be without prejudice to any rights or financial compensation that will have accrued to the benefit of a Party prior to such termination or expiration. Such termination or expiration will not relieve a Party from obligations that are expressly indicated to survive the termination or expiration of this Agreement. For purposes of clarification, milestone payments under ARTICLE 6 accrue as of the date the applicable Milestone Event is achieved even if the payment is not due at that time.

(e) **Survival**. The following provisions of this Agreement will survive the expiration or termination of this Agreement: Section 1.12 (Failure to Designate an Isis Development Candidate) (but only if this Agreement is terminated under Section 10.2.6(b) with respect to the Isis Development Candidate-R&D Plan); Section 4.1.2 (Brain Shuttle IP Licenses); Section 4.1.4(d) (Effect of Termination on Sublicenses), Section 4.2 (Technology Transfer after Option Exercise) (but only to the extent necessary to satisfy the requirements of Section 10.4.2), Section 6.10 (Reverse Royalty Payments to Roche for a Discontinued Product), Section 6.12.5 (Records Retention), Section 6.13 (Audits), Section 7.1.1 (Isis Technology and Roche Technology), Section 7.1.2 (Agreement Technology), Section 8.5 (Disclaimer), ARTICLE 9 (Indemnification; Insurance), Section 10.1 (Agreement Term; Expiration), Section 10.2.1 (Roche's Termination for Convenience), Section 10.2.5 (Termination for Insolvency), Section 10.4 (Consequences of Expiration or Termination of the Agreement), ARTICLE 11 (Confidentiality), ARTICLE 12 (Miscellaneous) and APPENDIX 1 (Definitions) (to the extent definitions are embodied in the foregoing listed Articles and Sections).

10.4.2. **Special Consequences of Expiration or Termination of the Agreement**. If (A) this Agreement expires due to the expiration of Roche's Option under Section 3.2, (B) Roche terminates the Agreement under Section 10.2.1 (Roche's Termination for Convenience), or (C) Isis terminates this Agreement under Section 7.12 (No Challenge), Section 10.2.2(b) (Isis' Right to Terminate) or Section 10.2.3(b) (Remedies for Failure to Use Commercially Reasonable Efforts), then the following additional terms will also apply:

(a) ***License to Isis for Isis Development Candidates***. Roche will and hereby does grant to Isis a sublicensable, worldwide, exclusive license or sublicense, as the case may be, under all Roche Technology (excluding Companion Diagnostic IP) Controlled by Roche as of the date of such reversion that Covers Discontinued Products comprising an Isis Development Candidate solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize such Discontinued Products in the Field;

(b) ***License to Isis for Brain Shuttle Development Candidates***. Roche will and hereby does grant to Isis a sublicensable, worldwide, non-exclusive license or sublicense, as the case may be, under all Roche Technology (excluding Companion Diagnostic IP) Controlled by Roche as of the date of such reversion that Covers Discontinued Products comprising a Brain Shuttle Development Candidate solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize such Discontinued Products in the Field;

(c) ***License to Isis for Companion Diagnostic Products***. Roche will make available to Isis, on commercially reasonable terms, any diagnostic products and/or services to select patients who will use Products (each, a "***Companion Diagnostic Product***") and any Patent Rights and Know-How Covering such Companion Diagnostic Products (such intellectual property, "***Companion Diagnostic IP***") Controlled by Roche as of the date of such reversion that is necessary to Develop or Commercialize such Companion Diagnostic Products;

(d) ***Know-How Transfer***. Roche will transfer to Isis for use with respect to the Development and Commercialization of Discontinued Products, copies of any Know-How data, results, regulatory information, filings, and files in the possession of Roche as of the date of such reversion that relate to such Discontinued Products and are necessary for the Development of such Discontinued Products, and any other information or material specified in Section 4.2;

(e) ***Trademarks***. Roche will license to Isis any trademarks that are specific to Discontinued Products solely for use with such Discontinued Products; *provided*, *however*, that in no event will Roche have any obligation to license to Isis any trademarks used by Roche both in connection with a Product and in connection with the sale of any other product or service, including any Roche- or Roche-formative marks, company logos, or trademarks of its Affiliates or Sublicensees; and

(f) ***Prosecution and Maintenance***. Isis will control and be responsible at its sole cost for all aspects of the Prosecution and Maintenance of all Jointly-Owned Collaboration Patents, and Roche will provide Isis with (and will instruct its counsel to provide Isis with) all of the information and records in Roche's and its counsel's possession related to the Prosecution and Maintenance of such Jointly-Owned Collaboration Patents.

ARTICLE 11.
CONFIDENTIALITY

11.1. **Confidentiality; Exceptions**. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that, during the Agreement Term and for five years thereafter, the receiving Party (the "***Receiving Party***") and its Affiliates will keep confidential and will not publish or otherwise disclose or use for any purpose other than as provided for in this Agreement any confidential or proprietary information or materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise) which is disclosed to it by the other Party (the "***Disclosing Party***") or its Affiliates or otherwise received or accessed by a Receiving Party in the course of performing its obligations or exercising its rights under this Agreement, including trade secrets, Know-How, inventions or discoveries, proprietary information, formulae, processes, techniques and information relating to the past, present and future marketing, financial, and research and development activities of any product or potential product or useful technology of the Disclosing Party or its Affiliates and the pricing thereof (collectively, "***Confidential Information***").

11.2. **Prior Confidentiality Agreement**. The Non-Disclosure Agreement executed by Isis and Roche on February 1, 2012 (including any and all amendments thereto) (the "***CDA***") will govern disclosures of Information (as defined in the CDA) between the Parties prior to the Effective Date. All Confidential Information exchanged between the Parties on or after the Effective Date under this Agreement will be subject to the terms of this ARTICLE 11.

11.3. **Authorized Disclosure**. Except as expressly provided otherwise in this Agreement, a Receiving Party or its Affiliates may use and disclose to Third Parties Confidential Information of the Disclosing Party as follows: (i) solely in connection with the performance of its obligations or exercise of rights granted or reserved in this Agreement under confidentiality provisions no less restrictive than those in this Agreement, *provided*, a Receiving Party may disclose Confidential Information to a governmental entity or agency without requiring such entity or agency to enter into a confidentiality agreement; (ii) to the extent reasonably necessary to file or prosecute patent, copyright and trademark applications (subject to Section 11.4 below), complying with applicable governmental regulations, obtaining Approvals, conducting Pre-Clinical Studies or Clinical Studies, marketing a Product, or as otherwise required by applicable law, regulation, rule or legal process (including the rules of the SEC and any stock exchange); *provided, however*, that if a Receiving Party or any of its Affiliates is required by law or regulation to make any such disclosure of a Disclosing Party's Confidential Information it will, except where impracticable for necessary disclosures, give reasonable advance notice to the Disclosing Party of such disclosure requirement and will use its reasonable efforts to secure confidential treatment of such Confidential Information required to be disclosed; (iii) in communication with actual or potential lenders, investors, merger partners, acquirers, consultants, or professional advisors on a need-to-know basis, in each case under confidentiality provisions no less restrictive than those of this Agreement; (iv) to the extent such disclosure is required to comply with existing expressly stated contractual obligations owed to such Party's or its Affiliates' licensor with respect to any intellectual property licensed to the other Party under this Agreement; or (v) as mutually agreed to in writing by the Parties.

11.4. **Press Release; Publications; Disclosure of Agreement**.

11.4.1. **Public Announcements – Generally**. Upon execution of this Agreement, the Parties will issue a joint press release announcing the existence of this Agreement in a form and substance agreed to in writing by the Parties. Except to the extent required to comply with Applicable Law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 11.4, each Party agrees not to issue any other press release or other public statement disclosing other information relating to this Agreement or the terms of this Agreement or the transactions contemplated hereby without the prior written consent of the other Party, which consent will not be unreasonably withheld or delayed.

11.4.2. **Use of Name**. Except as set forth in Section 11.4.9, neither Party will use the other Party's name in a press release or other publication without first obtaining the prior consent of the Party to be named.

11.4.3. **Notice of Significant Events**. Each Party will notify (no later than three Business Days after the information or results are obtained) the other Party of any significant event related to a Product (including any data, serious adverse event or regulatory advice or approval) so that the Parties may analyze the need to or desirability of publicly disclosing or reporting such event. Notwithstanding Section 11.4.1 above, any press release or other similar public communication by either Party related to a Product's efficacy or safety data and/or results, will be submitted to the other Party for review and approval at least three Business Days in advance of such proposed public disclosure, which approval will not be unreasonably withheld or delayed.

11.4.4. **Prior to Option Exercise**. Prior to Option exercise, Isis will have the sole right, consistent with its practice with its other compounds and products, to issue press releases, publish, present or otherwise disclose the progress and results regarding the Products to the public; *provided*, that with respect to any proposed press release or other similar public communication by Isis disclosing regulatory discussions, the efficacy or safety data or clinical results related to the Products, (i) Isis will submit such proposed communication to Roche for review at least ten (10) Business Days in advance of such proposed public disclosure, (ii) Roche will have the right to review and recommend changes to such communication, and (iii) Isis will in good faith consider any changes that are timely recommended by Roche.

11.4.5. **After Option Exercise**. After Option exercise, Roche will have the sole right, consistent with its practice with its other compounds and products, to issue press releases, publish, present or otherwise disclose the progress and results regarding the Products to the public; *provided*, that with respect to any proposed press release or other similar public communication by Roche disclosing regulatory discussions, the efficacy or safety data or results related to the Products or Roche's sales projections, (i) Roche will submit such proposed communication to Isis for review at least two Business Days in advance of such proposed public disclosure, (ii) Isis will have the right to review and recommend changes to such communication, and (iii) Roche will in good faith consider any changes that are timely recommended by Isis.

11.4.6. **Scientific or Clinical Presentations**. Regarding any proposed scientific publications related to results from any Clinical Studies, the Parties agree to use Commercially Reasonable Efforts to control public scientific disclosures of such results to prevent any adverse effect of any premature public disclosure of such results. The Parties will establish a procedure for publication review and each Party will first submit to the other Party through the Joint Patent Committee an early draft of all such publications or presentations, at least forty-five (45) days prior to submission for publication including to facilitate the publication of any summaries of Clinical Studies data and results as required on the clinical trial registry of each respective Party. Each Party will review such proposed publication to avoid the unauthorized disclosure of a Party's Confidential Information and to preserve the patentability of inventions arising from an R&D Plan. If, during such forty-five (45) day period, the other Party informs such Party that its proposed publication contains Confidential Information of the other Party, then such Party will delete such Confidential Information from its proposed publication. In addition, if during such forty-five (45) day period, the other Party informs such Party that its proposed publication discloses non-public inventions made by either Party in the course of the Development under this Agreement, or the public disclosure of such proposed publication may have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by such other Party, then such Party will either (i) delay such proposed publication for up to sixty (60) days from the date of such Party's objection, to permit the timely first filing of patent application(s), or (ii) remove the identified disclosures prior to publication.

11.4.7 **SEC Filings**. Each Party will give the other Party a reasonable opportunity to review all material filings with the SEC describing the terms of this Agreement prior to submission of such filings, and will give due consideration to any reasonable comments by the non-filing Party relating to such filing.

11.4.8 **Subsequent Disclosure**. Notwithstanding the foregoing, to the extent information regarding this Agreement or a Product has already been publicly disclosed, either Party (or its Affiliates) may subsequently disclose the same information to the public without the consent of the other Party.

11.4.9 **Acknowledgment; Commercial Materials**. Each Party will acknowledge in any press release, public presentation, publication or commercial marketing materials regarding the collaboration or a Product, the other Party's role in discovering and developing a Product or Discontinued Product, as applicable, that the Product is under license from Isis and otherwise acknowledge the contributions from the other Party, and each Party's stock ticker symbol (e.g., Isis: Nasdaq: ISIS; Roche: SIX: RO, ROG; OTCQX: RHHBY). Isis may include the Products (and identify Roche as its partner for the Product) in Isis' drug pipeline.

ARTICLE 12.
MISCELLANEOUS

12.1. **Dispute Resolution**.

12.1.1. **Escalation**. If any dispute occurs under this Agreement (other than a dispute regarding the construction, validity or enforcement of either Party's Patents, which disputes will be resolved pursuant to Section 12.2), either Party may request in writing that the dispute be referred for resolution to the Head of Roche Partnering of Roche and the COO of Isis (the "***Executives***"). Within thirty (30) days after such a request, the Executives will meet in person at a mutually acceptable time and location or by means of telephone or video conference to negotiate a settlement of the dispute. Each Party's JSC representatives may participate in such meeting if desired. If the Executives fail to resolve the dispute within such thirty (30) day period, then the dispute will be referred to binding arbitration under Section 12.1.2.

12.1.2. **Binding Arbitration**. If a dispute subject to Section 12.1.1 is not resolved pursuant to Section 12.1.1, such dispute will be resolved through binding arbitration in accordance with this Section 12.1.2 and under the Commercial Arbitration Rules of the American Arbitration Association ("***AAA***") then in effect, including application of the "*Expedited Procedures*" (sections E-1, et al) of the Commercial Arbitration Rules of the AAA. The proceedings and decisions of the arbitrator will be confidential, final and binding on the Parties, and judgment upon the award of such arbitrators may be entered in any court having jurisdiction thereof. The arbitration will take place in Boston, Massachusetts USA and will be conducted by three (3) arbitrators. Each of Roche and Isis shall appoint one (1) arbitrator within thirty (30) days after the notice that initiated the arbitration. These two (2) arbitrators shall in turn appoint a third arbitrator who will be reasonably acceptable to the Parties and who will be appointed in accordance with AAA rules. Each arbitrator chosen hereunder will have educational training and industry experience sufficient to demonstrate a reasonable level of scientific, financial, medical and industry knowledge relevant to the particular dispute.

12.2. **Governing Law; Jurisdiction; Venue; Service of Process**.

12.2.1. This Agreement and any dispute will be governed by and construed and enforced in accordance with the laws of the State of California, U.S.A., without reference to conflicts of laws principles.

12.2.2. Each Party hereby agrees that service of process: (a) made in any manner permitted by California law, or (b) made by overnight express courier service (signature required), prepaid, at its address specified pursuant to Section 12.7, will constitute good and valid service of process in any such action and (c) waives and agrees not to assert (by way of motion, as a defense, or otherwise) in any such action any claim that service of process made in accordance with clause (a) or (b) does not constitute good and valid service of process.

12.3. **Remedies**. Notwithstanding anything to the contrary in this Agreement, each Party will be entitled to seek, in addition to any other right or remedy it may have, at law or in equity, a temporary restraining order or a preliminary injunction, without the posting of any bond or other security, enjoining or restraining the other Party from any violation or threatened violation of this Agreement, and the Parties agree that in the event of a threatened or actual material breach of this Agreement injunctive relief would be appropriate. Neither Party may recover any Losses relating to any matter arising under one provision of this Agreement to the extent that such Party has already recovered Losses with respect to such matter pursuant to other provisions of this Agreement (including recoveries under Section 9.1 or Section 9.2). Except for the offsets and credits explicitly set forth in Section 6.11.3(b) and Section 6.13, neither Party will have the right to setoff any amount it is owed or believes it is owed against payments due or payable to the other Party under this Agreement.

12.4. **Assignment and Successors**. Neither this Agreement nor any obligation of a Party hereunder may be assigned by either Party without the consent of the other, except that each Party may assign this Agreement and the rights, obligations and interests of such Party, in whole or in part, without the other Party's consent, to any of its Affiliates, to any purchaser of all or substantially all of its assets or all or substantially all of its assets to which this Agreement relates or to any successor corporation resulting from any merger, consolidation, share exchange or other similar transaction; *provided*, if a Party transfers or assigns this Agreement to [***] described in this Agreement, then such transferring Party (or such Affiliate) ("***Transferring Party***"), will [***] that the Transferring Party is obligated to pay to the non-transferring Party ("***Non-Transferring Party***") under ARTICLE 6 for the taxes withheld such that the Non-Transferring Party receives [***] assignment. In addition, Isis may assign or transfer its rights to receive payments under this Agreement (but no liabilities), without Roche's consent, to an Affiliate or to a Third Party in connection with a payment factoring transaction. Any purported assignment or transfer made in contravention of this Section 12.4 will be null and void.

To the extent the Non-Transferring Party utilizes a [***] in any year, the Non-Transferring Party will [***] to the Transferring Party [***]. To assist the Transferring Party in determining when [***] pursuant to the foregoing sentence, beginning with the first Annual tax return for the year in which the [***] payment under this Section 12.4, and each year thereafter (including, for clarity, all years in which the Non-Transferring Party utilizes a [***]), the Non-Transferring Party will provide the Transferring Party with the Non-Transferring Party s' Annual tax returns (federal and state) and, in years in which the Non-Transferring Party utilizes the [***], supporting documentation for such [***].

12.5. **Change of Control**. If Isis undergoes a Change of Control, then Roche shall have the right at any time after it exercises the Option to disband the JSC and make unilateral decisions with respect to the R&D Plan, Development and Commercialization with no obligation to seek input from Isis or its successor, if applicable.

12.6. **Force Majeure**. No Party will be held responsible to the other Party nor be deemed to be in default under, or in breach of any provision of, this Agreement for failure or delay in performing any obligation of this Agreement when such failure or delay is due to force majeure, and without the fault or negligence of the Party so failing or delaying. For purposes of this Agreement, force majeure means a cause beyond the reasonable control of a Party, which may include acts of God; acts, regulations, or laws of any government; war; terrorism; civil commotion; fire, flood, earthquake, tornado, tsunami, explosion or storm; pandemic; epidemic and failure of public utilities or common carriers. In such event the Party so failing or delaying will immediately notify the other Party of such inability and of the period for which such inability is expected to continue. The Party giving such notice will be excused from such of its obligations under this Agreement as it is thereby disabled from performing for so long as it is so disabled for up to a maximum of ninety (90) days, after which time the Parties will negotiate in good faith any modifications of the terms of this Agreement that may be necessary to arrive at an equitable solution, unless the Party giving such notice has set out a reasonable timeframe and plan to resolve the effects of such force majeure and executes such plan within such timeframe. To the extent possible, each Party will use reasonable efforts to minimize the duration of any force majeure.

12.7. **Notices**. Any notice or request required or permitted to be given under or in connection with this Agreement will be deemed to have been sufficiently given if in writing and personally delivered or sent by certified mail (return receipt requested), facsimile transmission (receipt verified), or overnight express courier service (signature required), prepaid, to the Party for which such notice is intended, at the address set forth for such Party below:

If to Isis, addressed to:

Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Operating Officer
Fax: 760-918-3592

with a copy to:

Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: General Counsel
Fax: 760-268-4922

If to Roche, addressed to:

F. Hoffmann-La Roche Ltd
Grenzacherstrasse 124
4070 Basel, Switzerland
Attention: Corporate Legal Department
Fax: +41 61 688 13 96

If to Roche, addressed to:

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110
Attention: Corporate Secretary
Fax: 973-235-3500

with a copy to:

F. Hoffmann-La Roche Ltd
Grenzacherstrasse 124
4070 Basel, Switzerland
Attention: Alliance Manager
Fax: +41 61 688 30 50

or to such other address for such Party as it will have specified by like notice to the other Party; *provided that* notices of a change of address will be effective only upon receipt thereof. If delivered personally or by facsimile transmission, the date of delivery will be deemed to be the date on which such notice or request was given. If sent by overnight express courier service, the date of delivery will be deemed to be the next Business Day after such notice or request was deposited with such service. If sent by certified mail, the date of delivery will be deemed to be the third Business Day after such notice or request was deposited with the U.S. Postal Service.

12.8. **Invoices**. All invoices that are required or permitted hereunder shall be in writing and sent by Isis to Roche at the following address or any other address that Roche may later provide:

F. Hoffmann-La Roche AG
Kreditorenbuchhaltung
4070 Basel
Switzerland

with an electronic copy to Roche's Alliance Manager.

Upon Isis' request, Roche's Alliance Manager will provide Isis' Alliance Manager with any additional information reasonably requested by Isis to facilitate the prompt delivery of invoices to Roche, including a facsimile number for sending invoices.

12.9. **Export Clause**. Each Party acknowledges that the laws and regulations of the United States restrict the export and re-export of commodities and technical data of United States origin. Each Party agrees that it will not export or re-export restricted commodities or the technical data of the other Party in any form without the appropriate United States and foreign government licenses.

12.10. **Waiver**. Neither Party may waive or release any of its rights or interests in this Agreement except in writing. The failure of either Party to assert a right hereunder or to insist upon compliance with any term or condition of this Agreement will not constitute a waiver of that right or excuse a similar subsequent failure to perform any such term or condition. No waiver by either Party of any condition or term in any one or more instances will be construed as a continuing waiver or subsequent waiver of such condition or term or of another condition or term.

12.11. **Severability**. If any provision hereof should be held invalid, illegal or unenforceable in any jurisdiction, the Parties will negotiate in good faith a valid, legal and enforceable substitute provision that most nearly reflects the original intent of the Parties and all other provisions hereof will remain in full force and effect in such jurisdiction and will be liberally construed in order to carry out the intentions of the Parties hereto as nearly as may be possible. Such invalidity, illegality or unenforceability will not affect the validity, legality or enforceability of such provision in any other jurisdiction.

12.12. **Entire Agreement**. This Agreement, together with the Schedules and Appendices hereto, sets forth all the covenants, promises, agreements, warranties, representations, conditions and understandings between the Parties and supersedes and terminates all prior agreements and understanding between the Parties. There are no covenants, promises, agreements, warranties, representations, conditions or understandings, either oral or written, between the Parties other than as set forth herein and therein. No subsequent alteration, amendment, change or addition to this Agreement will be binding upon the Parties hereto unless reduced to writing and signed by the respective authorized officers of the Parties.

12.13. **Independent Contractors**. Nothing herein will be construed to create any relationship of employer and employee, agent and principal, partnership or joint venture between the Parties. Each Party is an independent contractor. Neither Party will assume, either directly or indirectly, any liability of or for the other Party. Neither Party will have the authority to bind or obligate the other Party and neither Party will represent that it has such authority.

12.14. **Interpretation**. Except as otherwise explicitly specified to the contrary, (a) references to a section, exhibit or schedule means a section of, or schedule or exhibit to this Agreement, unless another agreement is specified, (b) the word "including" (in its various forms) means "including without limitation," (c) the words "will" and "shall" have the same meaning, (d) references to a particular statute or regulation include all rules and regulations thereunder and any predecessor or successor statute, rules or regulation, in each case as amended or otherwise modified from time to time, (e) words in the singular or plural form include the plural and singular form, respectively, (f) references to a particular Person include such Person's successors and assigns to the extent not prohibited by this Agreement, (g) unless otherwise specified, "$" is in reference to United States dollars, and (h) the headings contained in this Agreement, in any exhibit or schedule to this Agreement and in the table of contents to this Agreement are for convenience only and will not in any way affect the construction of or be taken into consideration in interpreting this Agreement.

12.15. **Further Actions**. Each Party will execute, acknowledge and deliver such further instruments, and do all such other acts, as may be necessary or appropriate in order to carry out the expressly stated purposes and the clear intent of this Agreement.

12.16. **Construction of Agreement**. The terms and provisions of this Agreement represent the results of negotiations between the Parties and their representatives, each of which has been represented by counsel of its own choosing, and neither of which has acted under duress or compulsion, whether legal, economic or otherwise. Accordingly, the terms and provisions of this Agreement will be interpreted and construed in accordance with their usual and customary meanings, and each of the Parties hereto hereby waives the application in connection with the interpretation and construction of this Agreement of any rule of law to the effect that ambiguous or conflicting terms or provisions contained in this Agreement will be interpreted or construed against the Party whose attorney prepared the executed draft or any earlier draft of this Agreement.

12.17. **Supremacy**. In the event of any express conflict or inconsistency between this Agreement and any Schedule or Appendix hereto, the terms of this Agreement will apply. The Parties understand and agree that the Schedules and Appendices hereto are not intended to be the final and complete embodiment of any terms or provisions of this Agreement, and are to be updated from time to time during the Agreement Term, as appropriate and in accordance with the provisions of this Agreement.

12.18. **Counterparts**. This Agreement may be signed in counterparts, each of which will be deemed an original, notwithstanding variations in format or file designation which may result from the electronic transmission, storage and printing of copies of this Agreement from separate computers or printers. Facsimile signatures and signatures transmitted via electronic mail in PDF format will be treated as original signatures.

[SIGNATURE PAGES FOLLOW]

* - * - * - *

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their representatives thereunto duly authorized as of the Effective Date.

F. HOFFMANN-LA ROCHE LTD

By: _____
Name:
Title:

By: _____
Name:
Title:

SIGNATURE PAGE TO HTT RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their representatives thereunto duly authorized as of the Effective Date.

HOFFMANN-LA ROCHE INC.

By: _____
Name:
Title:

SIGNATURE PAGE TO HTT RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their representatives thereunto duly authorized as of the Effective Date.

ISIS PHARMACEUTICALS, INC.

By: _____
Name: B. Lynne Parshall
Title: Chief Operating Officer

SIGNATURE PAGE TO HTT RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT

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APPENDIX 1

DEFINITIONS

For purposes of this Agreement, the following capitalized terms will have the following meanings:

"***Acceptance***" means, with respect to an NDA, MAA or JNDA filed for a Product, (a) in the United States, the receipt of written notice from the FDA in accordance with 21 C.F.R. §314.101(a)(2) that such NDA is officially "*filed*," (b) in the European Union, receipt of written notice of acceptance by the EMA of such MAA for filing under the centralized European procedure in accordance with any feedback received from European Regulatory Authorities; *provided that* if the centralized filing procedure is not used, then Acceptance will be determined upon the acceptance of such MAA by the applicable Regulatory Authority in a Major Market in the EU, and (c) in Japan, receipt of written notice of acceptance of filing of such JNDA from the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***Additional Core IP***" has the meaning set forth in Section 6.11.3(a).

"***Additional Costs***" means [***].

"***Additional Isis Development Candidate-Cost Estimate***" has the meaning set forth in Section 1.8.3.

"***Additional Isis In-License Agreements***" has the meaning set forth in Section 6.11.1(b).

"***Additional Product-Specific Patents***" has the meaning set forth in Section 6.11.2(a).

"***Affiliate***" of an entity means any corporation, firm, partnership or other entity which directly or indirectly through one or more intermediaries controls, is controlled by or is under common control with a Party to this Agreement. An entity will be deemed to control another entity if it (i) owns, directly or indirectly, more than fifty percent (50%) of the outstanding voting securities or capital stock (or such lesser percentage which is the maximum allowed to be owned by a foreign corporation in a particular jurisdiction) of such other entity, or has other comparable ownership interest with respect to any entity other than a corporation; or (ii) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the entity. Anything to the contrary in this paragraph notwithstanding, Chugai Pharmaceutical Co., Ltd, a Japanese corporation ("Chugai"), shall not be deemed an Affiliate of Roche unless Roche provides written notice to Isis of its desire to include Chugai as an Affiliate of Roche.

"***Agreement***" has the meaning set forth in the Preamble of this Agreement.

"***Agreement Term***" has the meaning set forth in Section 10.1.

"***Alliance Manager***" has the meaning set forth in Section 1.5.3.

"***ANDA***" means an Abbreviated New Drug Application and all amendments and supplements thereto filed with the FDA, or the equivalent application filed with any equivalent agency or governmental authority outside the U.S. (including any supra-national agency such as the EMA in the EU).

"***Annual***" means the period covering a Calendar Year or occurring once per Calendar Year, as the context requires.

"***API***" means the bulk active pharmaceutical ingredient manufactured in accordance with cGMP for a Product.

"***Applicable Law***" or "***Law***" means all applicable laws, statutes, rules, regulations and other pronouncements having the effect of law of any federal, national, multinational, state, provincial, county, city or other political subdivision, agency or other body, domestic or foreign, including any applicable rules, regulations, guidelines, or other requirements of the Regulatory Authorities that may be in effect from time to time.

"***Approval***" means (i) with respect to a Product in the EU, the earlier to occur of (A) approval from the applicable Regulatory Authority in at least one member state in the EU sufficient for the manufacture, distribution, use, marketing and sale of such Product, including pricing and reimbursement approval, in such jurisdiction in accordance with Applicable Laws, or (B) the First Commercial Sale of a Product in the EU; and (ii) with respect to a Product in any regulatory jurisdiction other than the EU, approval sufficient for the manufacture, distribution, use, marketing and sale of such Product in such jurisdiction in accordance with Applicable Laws.

"***Approved Changes***" means any changes (including number of subjects, duration of dosing, additional studies, additional endpoints, additional analysis, etc.) to the Isis Development Candidate-R&D Plan that are agreed to by Roche (including any changes required by a Regulatory Authority).

"***AS ASO***" has the meaning set forth in Section 2.1.1(b)(ii).

"***AS Development Candidate***" has the meaning set forth in Section 2.1.1(b)(ii).

"***ASO***" means an oligonucleotide compound, or analog, variant, mimic, or mimetic thereof, having a sequence that is at least six bases long and that modulates expression or splicing of a gene target via the binding, partially or wholly, of such compound to the RNA of such gene target.

"***ASO-Specific Collaboration Patents***" has the meaning set forth in Section 7.1.3(a).

"***Audit Report***" has the meaning set forth in Section 6.13.

"***Back-Up Compound***" means a Compound (other than the first Development Candidate) that was used in any monkey tolerability screen performed to identify the first Development Candidate.

"***Bankruptcy Code***" has the meaning set forth in Section 10.2.5(b).

"***Brain Shuttle***" has the meaning set forth in Section 1.1.

"***Brain Shuttle Collaboration Patents***" means Patent Rights arising under the Brain Shuttle Development Candidate-R&D Plan after the Effective Date that are Controlled by a Party or any of its Affiliates. The Parties will list on APPENDIX 6 the Brain Shuttle Collaboration Patents, and will update APPENDIX 6 when additional Brain Shuttle Collaboration Patents arise under the Brain Shuttle Development Candidate-R&D Plan.

"***Brain Shuttle Development Candidate***" has the meaning set forth in Section 1.3.1.

"***Brain Shuttle Development Candidate-R&D Plan***" means the research and development plan attached hereto as APPENDIX 3 (as may be amended in accordance with this Agreement) to conduct the Isis R&D Activities and Roche R&D Activities designated under such plan focused on the research and development of a Brain Shuttle Development Candidate.

"***Brain Shuttle Development Candidate Reverse Royalties***" has the meaning set forth in Section 6.10.2.

"***Brain Shuttle Program Cost Estimate***" has the meaning set forth in Section 1.6.2(b)(i).

"***Brain Shuttle-Specific Collaboration Patents***" has the meaning set forth in Section 7.1.3(a).

"***Brain Shuttle Technology***" means the Brain Shuttle technology disclosed in the Roche Existing Brain Shuttle Patents listed on Schedule 8.4.1 or otherwise existing as of the Effective Date as evidenced by Roche's written records.

"***Breaching Party***" means the Party that is believed by the Non-Breaching Party to be in material breach of this Agreement.

"***Business Day***" means any day other than a Saturday or Sunday on which banking institutions in New York, New York are open for business.

"***Calendar Quarter***" means a period of three consecutive months ending on the last day of March, June, September, or December, respectively, and will also include the period beginning on the Effective Date and ending on the last day of the Calendar Quarter in which the Effective Date falls.

"***Calendar Year***" means a year beginning on January 1 (or, with respect to 2013, the Effective Date) and ending on December 31.

"***CDA***" has the meaning set forth in Section 11.2.

"***cGMP***" means current Good Manufacturing Practices as specified in the United States Code of Federal Regulations, ICH Guideline Q7A, or equivalent laws, rules, or regulations of an applicable Regulatory Authority at the time of manufacture.

"***Change of Control***" means, with respect to a Party: (a) the acquisition by any Third Party of beneficial ownership of more than fifty percent (50%) of the then outstanding common shares or voting power of such Party, other than acquisitions by employee benefit plans sponsored or maintained by such Party; (b) the consummation of a business combination involving such Party, unless, following such business combination, the stockholders of such Party immediately prior to such business combination beneficially own directly or indirectly more than fifty percent (50%) of the then outstanding common shares or voting power of the entity resulting from such business combination.

"***Change Overruns***" has the meaning set forth in Section 1.6.1(b).

"***CHDI***" means the CHDI Foundation, Inc.

"***Claims***" has the meaning set forth in Section 9.1.

"***Clinical Study***" or "***Clinical Studies***" means a Phase 1 Trial, Phase 2 Trial, Registration-Directed Trial or Phase 4 Trial, or such other study in humans that is conducted in accordance with good clinical practices and is designed to generate data in support or maintenance of an NDA, MAA, JNDA or other similar marketing application.

"***CMO***" means a Third Party contract manufacturer Manufacturing API or finished drug Product for any purpose under this Agreement.

"***Collaboration***" means the conduct of research and development of a Compound, Isis Development Candidate, or Brain Shuttle Development Candidate (as applicable), in each case in accordance with the applicable R&D Plan.

"***Collaboration Patents***" means collectively Roche Collaboration Patents, Isis Collaboration Patents and Jointly-Owned Collaboration Patents.

"***Commercialize***," "***Commercialization***" or "***Commercializing***" means any and all activities directed to marketing, promoting, detailing, distributing, importing, having imported, exporting, having exported, selling or offering to sell a Product following receipt of Approval for a Product in the applicable country, including conducting pre-and post-Approval activities, including studies reasonably required to increase the market potential of a Product and studies to provide improved formulation and Product delivery, and launching and promoting a Product in each country.

"***Commercializing Party***" means (a) Roche, with respect to a Product that is being Developed and Commercialized by or on behalf of Roche, its Affiliates or Sublicensees hereunder, and (b) Isis, with respect to a Discontinued Product that is being Developed and Commercialized by or on behalf of Isis, its Affiliates or Sublicensees hereunder.

"***Commercially Reasonable Efforts***" means the carrying out of discovery, research, development or commercialization activities using good-faith commercially reasonable and diligent efforts that the applicable Party would reasonably devote to a compound or product of similar market potential or profit potential at a similar stage in development or product life resulting from its own research efforts, based on conditions then prevailing and taking into account, without limitation, issues of safety and efficacy, regulatory authority-approved labeling, product profile, the competitiveness of alternative products in the marketplace, the likely timing of the product's entry into the market, the patent and other proprietary position, the likelihood of approval and other relevant scientific, technical and commercial factors. The Isis Development Candidate-R&D Plan attached to this Agreement as of the Effective Date as Appendix 2 exemplifies a level of diligence that meets the Commercially Reasonable Efforts standard required under this Agreement. Without limiting any of the foregoing, (A) Commercially Reasonable Efforts as it applies to Roche's Development or Commercialization of a Product hereunder includes the use of Commercially Reasonable Efforts to (i) perform the Roche R&D Activities designated under the R&D Plans in accordance with the timelines set forth therein, (ii) perform the activities set forth in each IDCP in accordance with the timelines set forth therein, (iii) perform the "*General Activities*" set forth in Appendix 5, and (iv) achieve the specific performance milestone events set forth in Appendix 5 ("***Specific Performance Milestone Events***") for a Product on the timeline set forth in Appendix 5; *provided*, *however*, if (X) regulatory or Development issues arise that are outside of Roche's reasonable control and make achievement of any such Specific Performance Milestone Event on the stated timeline impossible, or (Y) an Isis Development Candidate is being Developed but Roche subsequently decides to Develop a Brain Shuttle Development Candidate in lieu of such Isis Development Candidate, the Parties will meet and negotiate in good faith to revise, consistent with any applicable Isis In-License Agreements, the date by which the applicable Specific Performance Milestone Event must be achieved; and (B) Commercially Reasonable Efforts as it applies to Isis' Development of a Product hereunder includes use of Commercially Reasonable Efforts to perform the Isis R&D Activities designated under the R&D Plans in accordance with the timelines set forth therein. However, Roche (and its Affiliates) does not always seek to market its own products in every country or seek to obtain regulatory approval in every country or for every potential indication. As a result, the exercise of diligence by Roche is to be determined by judging Roche's commercially reasonable efforts in the Major Markets, taken as a whole.

"***Companion Diagnostic IP***" has the meaning set forth in Section 10.4.2(c).

"***Companion Diagnostic Product***" has the meaning set forth in Section 10.4.2(c).

"***Competitive Infringement***" has the meaning set forth in Section 7.5.1.

"***Compound***" means an ASO that is designed to bind to (i) the RNA that encodes HTT (such ASO, a "***Non-Allele Selective Compound***"); or (ii) a SNP site within an HTT RNA that is associated with an expanded CAG repeat to selectively reduce the expanded CAG-repeat containing RNA relative to the normal HTT RNA via an RNase H dependent mechanism (such ASO, an "***Allele Selective Compound***"), in each case where such ASO is discovered by Isis prior to or in the performance of an R&D Plan.

"***Compulsory Sublicense***" means a Sublicense granted to a Third Party, through the order, decree or grant of a governmental authority having competent jurisdiction, authorizing such Third Party to manufacture, use, sale, offer for sale, import or export a Product in any country.

"***Compulsory Sublicensee***" means a Third Party that was granted a Compulsory Sublicense.

"***Confidential Information***" has the meaning set forth in Section 11.1. "*Confidential Information*" does not include information that:

(a) was in the lawful knowledge and possession of the Receiving Party or its Affiliates prior to the time it was disclosed to, or learned by, the Receiving Party or its Affiliates, or was otherwise developed independently by the Receiving Party or its Affiliates, as evidenced by written records kept in the ordinary course of business, or other documentary proof of actual use by the Receiving Party or its Affiliates;

(b) was generally available to the public or otherwise part of the public domain at the time of its disclosure to the Receiving Party or its Affiliates;

(c) became generally available to the public or otherwise part of the public domain after its disclosure and other than through any act or omission of the Receiving Party or its Affiliates in breach of this Agreement; or

(d) was disclosed to the Receiving Party or its Affiliates, other than under an obligation of confidentiality, by a Third Party who had no obligation to the Disclosing Party or its Affiliates not to disclose such information to others.

"***Control***" or "***Controlled***" means possession of the ability to grant a license or sublicense hereunder without violating the terms of any agreement with any Third Party; *provided, however*, that if a Party has a right to grant a license or sublicense, with respect to an item of intellectual property to the other Party only upon payment of compensation (including milestones or royalties) to a Third Party ("***Third Party Compensation***") (other than Isis Supported Pass-Through Costs in the case of Isis, and other than Roche Supported Pass-Through Costs in the case of Roche), then the first Party will be deemed to have "*Control*" of the relevant item of intellectual property only if the other Party agrees to bear the cost of such Third Party Compensation. Notwithstanding anything to the contrary under this Agreement, with respect to any Third Party that becomes an Affiliate of a Party after the Effective Date (including a Third Party acquirer), no intellectual property of such Third Party will be included in the licenses granted hereunder by virtue of such Third Party becoming an Affiliate of such Party.

"***Cover***," "***Covered***" or "***Covering***" means, with respect to a patent, that the act of making, using or selling by an unauthorized Person would infringe a Valid Claim included in such patent, or in the case of a patent that is a patent application, would infringe a Valid Claim in such patent application if it were to issue as a patent.

"***CREATE Act***" means the Cooperative Research and Technology Enhancement Act of 2004, 35 U.S.C. § 103(c)(2)-(c)(3).

"***Develop***," "***Developing***" or "***Development***" means with respect to a Product, any and all discovery, characterization, or preclinical (including IND-Enabling Toxicology Studies), clinical, or regulatory activity with respect to a Product to seek Approval (including the submission of all necessary filings with applicable Regulatory Authorities to support such preclinical and clinical activities and Approval), including human clinical trials conducted after Approval of a Product to seek Approval for additional indications for a Product.

"***Development Candidate***" means (i) a Brain Shuttle Development Candidate, or (ii) an Isis Development Candidate.

"***Development Candidate Data Package***" means, with respect to [***] the [***]; *provided* such package contains the [***]. The checklist Isis uses as of the Effective Date when reviewing potential development candidates for approval is attached hereto as APPENDIX 4.

"***Disclosing Party***" has the meaning set forth in Section 11.1.

"***Discontinued Product***" means a Product that is the subject of a termination under this Agreement.

"***Effective Date***" has the meaning set forth in the Preamble of this Agreement.

"***EMA***" means the European Medicines Agency and any successor entity thereto.

"***European Union***" or "***EU***" means each and every country or territory that is officially part of the European Union.

"***Executives***" has the meaning set forth in Section 12.1.1.

"***Existing Diagnostic Agreement***" means that certain Non-Exclusive G-Clamp License Agreement between Isis and F. Hoffmann-La Roche Ltd dated April 26, 2011.

"***FDA***" means the United States Food and Drug Administration and any successor entity thereto.

"***FDCA***" shall mean the United States Food, Drug and Cosmetics Act.

"***Field***" means the prophylactic or therapeutic use or form of administration of a Product for any indication.

"***First Commercial Sale***" means the first sale of a Product by Roche, its Affiliate or its Sublicensee to a Third Party in a particular country after Approval of a Product has been obtained in such country.

"***FTE***" means a total of forty-seven (47) weeks or one thousand eight hundred eighty (1,880) hours per year of work on the Development of a Product carried out by employees of a Party having the appropriate relevant expertise to conduct such activities.

"***FTE Rate***" means [***]. The FTE Rate will be prorated for the actual portion of the full year the employee works under this Agreement. The FTE Rate will be increased each Calendar Year after 2013 by the [***].

"***Full Royalty Period***" has the meaning set forth in Section 6.7.2(a).

"***Fully Absorbed Cost of Goods***" means the costs incurred by Isis as determined using the methodology set forth in SCHEDULE 1.7.1 fairly applied and as employed on a consistent basis throughout Isis' operations.

"***Generic Product***" means the product(s) of one or more Third Party that is not a Sublicensee, which has the same active pharmaceutical ingredient as a Product and for which in the U.S. an ANDA has been filed naming such Product as the reference listed drug or outside of the U.S., an equivalent process where bioequivalence to such Product has been asserted.

"***Group Sublicensee***" means any individual, corporation, association or other business entity:

(i) to which Roche has granted a Sublicense;

(ii) that is not an Affiliate of Roche; and

(iii) that is consolidated within Roche's externally published audited financial statements.

"***HSR Act***" means Section 7A of the Clayton Act, as added by Title II of the Hart-Scott-Rodino Antitrust Improvement Act of 1976, as amended, and the rules and regulations promulgated thereunder.

"***Huntingtin***" or "***HTT***" means the human gene known as IT15 or HD (GenBank accession #NM_002111.5), or any alternative splice variants, mutants, polymorphisms and fragments thereof.

"***Huntington's Disease***" or "***HD***" means the hereditary disorder caused by mutation associated with trinucleotide repeat expansion in the Huntingtin gene on chromosome 4p.

"***IDCP***" has the meaning set forth in Section 5.1.

"***IND***" means an Investigational New Drug Application (as defined in the Food, Drug and Cosmetic Act, as amended) filed with the FDA or its foreign counterparts.

"***IND-Enabling Toxicology Studies***" means the pre-clinical studies required to file an IND.

"***Indemnitee***" has the meaning set forth in Section 9.3.

"***Independent Expert***" has the meaning set forth Section 5.1.1.

"***Initiation***" or "***Initiate***" means, (i) with respect to any IND-Enabling Toxicology Study, dosing of the first animal subject in such IND-Enabling Toxicology Study, (ii) with respect to any Clinical Study performed by Roche, its Affiliates or Sublicensees, the date the first patient is dosed with a Product in such Clinical Study, and (iii) with respect to any Clinical Study performed by Isis, its Affiliates or Sublicensees (excluding Roche), the date the first clinical trial site is approved by the applicable Reviewing Entity to participate in such Clinical Study.

"***Isis***" has the meaning set forth in the Preamble of this Agreement.

"***Isis Collaboration Know-How***" means Know-How discovered, developed, invented or created solely by or on behalf of Isis or its Affiliate or a Third Party acting on their behalf in the performance of an R&D Plan, that is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Isis Collaboration Patents***" means Patent Rights discovered, developed, invented or created solely by or on behalf of Isis or its Affiliate or a Third Party acting on their behalf in the performance of an R&D Plan, that are necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Isis Core Brain Shuttle Collaboration Patent***" has the meaning set forth in Section 7.2.2(a)(i).

"***Isis Core Technology Patents***" means all Patent Rights owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term, claiming subject matter generally applicable to ASOs, other than Isis Product-Specific Patents or Isis Manufacturing and Analytical Patents. A list of Isis Core Technology Patents as of the Effective Date is set forth on SCHEDULE 8.2.4(a) attached hereto.

"***Isis Development Candidate***" means a Compound that arises out of the Isis Development Candidate-R&D Plan that is reasonably determined by Isis' RMC in accordance with Isis' standard procedures for designating development candidates (and giving good faith consideration to the input of Roche's representatives on the JSC) as ready to start IND-Enabling Toxicology Studies. The checklist Isis uses as of the Effective Date when reviewing potential development candidates for approval is attached hereto as APPENDIX 4. The first Isis Development Candidate to be designated a Development Candidate hereunder is referred to throughout this Agreement as the "*first*" Isis Development Candidate. Any work on one or more additional or replacement Isis Development Candidates may be performed under an amended Isis Development Candidate-R&D Plan as contemplated by Section 1.8.

"***Isis Development Candidate-R&D Plan***" means the research and development plan attached hereto as APPENDIX 2 (as may be amended in accordance with this Agreement) to conduct the Isis R&D Activities and Roche R&D Activities designated under such plan focused on the research and development of an Isis Development Candidate.

"***Isis Development Candidate Reverse Royalties***" has the meaning set forth in Section 6.10.1.

"***Isis In-License Agreements***" has the meaning set forth in Section 6.11.1(a).

"***Isis Internal ASO Safety Database***" has the meaning set forth in Section 5.2.2(a).

"***Isis Know-How***" means any Know-How, including Isis' interest in any Jointly-Owned Collaboration Know-How, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. Isis Know-How does not include the Isis Manufacturing and Analytical Know-How.

"***Isis Manufacturing and Analytical Know-How***" means Know-How, including Isis' interest in any Jointly-Owned Collaboration Know-How, that relates to the synthesis or analysis of a Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. Isis Manufacturing and Analytical Know-How does not include the Isis Know-How.

"***Isis Manufacturing and Analytical Patents***" means Patent Rights, including Isis' interest in any Jointly-Owned Collaboration Patents, that claim methods and materials used in the synthesis or analysis of a Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Isis Manufacturing and Analytical Patents as of the Effective Date is set forth on SCHEDULE 8.2.4(b) attached hereto. Isis Manufacturing and Analytical Patents do not include the Isis Product-Specific Patents or the Isis Core Technology Patents.

"***Isis Product-Specific Brain Shuttle Collaboration Patent***" has the meaning set forth in Section 7.2.2(a)(ii).

"***Isis Product-Specific Patents***" means Patent Rights Controlled by Isis or any of its Affiliates on or after the Effective Date claiming (i) the specific composition of matter of an Isis Development Candidate; (ii) methods of using an Isis Development Candidate as a prophylactic or therapeutic; or (iii) the specific mechanism of action of an Isis Development Candidate, in each case to the extent necessary to Develop, Manufacture or Commercialize an Isis Development Candidate; *provided however*, Patent Rights Controlled by Isis or any of its Affiliates that (y) include claims that are directed to subject matter applicable to ASOs in general, or (z) include an ASO, the sequence of which targets both (a) the RNA that encodes HTT and (b) ASOs that do not target the RNA encoding HTT, will not be considered Isis Product-Specific Patents, and in the case of (y) and (z), such Patent Rights will be considered Isis Core Technology Patents. A list of Isis Product-Specific Patents as of the Effective Date is set forth on SCHEDULE 8.2.4(c) attached hereto.

"***Isis R&D Activities***" means the research, pre-clinical and/or clinical activities for which Isis is designated as responsible under an R&D Plan.

"***Isis Supported Pass-Through Costs***" means the licensing costs and payments payable by Isis to Third Parties to the extent arising from a Third Party agreement under [***].

"***Japan NDA***" or "***JNDA***" means the Japanese equivalent of an NDA filed with the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***JNDA Approval***" means the Approval of a JNDA by the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto) for the applicable Product in Japan.

"***Joint Patent Committee***" or "***JPC***" has the meaning set forth in Section 7.1.3(a).

"***Jointly-Owned Collaboration Know-How***" means Know-How discovered, developed, invented or created jointly in the performance of an R&D Plan by or on behalf of both Parties or their respective Affiliates or Third Parties acting on their behalf that is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Jointly-Owned Collaboration Patents***" means any Patent Rights discovered, developed, invented or created jointly in the performance of an R&D Plan by or on behalf of both Parties or their respective Affiliates or Third Parties acting on their behalf that is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Jointly-Owned Collaboration Technology***" means Jointly-Owned Collaboration Know-How and Jointly-Owned Collaboration Patents.

"***JSC***" has the meaning set forth in Section 1.5.1.

"***Know-How***" means unpatented inventions, technical information, know-how and materials, including technology, data, compositions, formulas, biological materials, assays, reagents, constructs, compounds, discoveries, procedures, processes, practices, protocols, methods, techniques, results of experimentation or testing, knowledge, trade secrets, skill and experience.

"***Lead Party***" has the meaning set forth in Section 7.4.1.

"***Licensed CMO***" has the meaning set forth in Section 4.1.4(a)(ii).

"***Licensed Know-How***" means Isis Manufacturing and Analytical Know-How, Isis Know-How, Isis Collaboration Know-How, and Isis' interest in any Jointly-Owned Collaboration Know-How. For clarity, Licensed Know-How does not include any Know-How covering formulation technology or delivery devices *unless* such Know-How is included in any Isis Collaboration Know-How or Jointly-Owned Collaboration Know-How.

"***Licensed Patents***" means the Isis Product-Specific Patents, Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, Isis Collaboration Patents, and Isis' interest in any Jointly-Owned Collaboration Patents and Brain Shuttle Collaboration Patents. For clarity, Licensed Patents do not include any Patent Rights claiming formulation technology or delivery devices *unless* such Patent Rights are included in any Isis Collaboration Patents or Jointly-Owned Collaboration Patents.

"***Licensed Technology***" means any and all Licensed Patents and Licensed Know-How, in each case to the extent necessary or useful to Develop, Manufacture or Commercialize a Product. "*Licensed Technology*" expressly excludes all technology licensed to Isis under the UTSW Agreement because such technology is not utilized by, nor does it cover, the Compounds.

"***Linker-Specific Collaboration Patents***" has the meaning set forth in Section 7.1.3(a).

"***Losses***" has the meaning set forth in Section 9.1.

"***MAA***" means a marketing authorization application filed with the EMA after completion of Clinical Studies to obtain Approval for a Product under the centralized European filing procedure or, if the centralized EMA filing procedure is not used, filed using the applicable procedures in any European Union country.

"***MAA Approval***" means the Approval of an MAA by the EMA for a Product in any country in the EU.

"***Major Market***" means any of the following countries: the United States, Japan, the United Kingdom, Germany, France, Italy, Spain, Brazil, Russia, India and China.

"***Manufacture***" or "***Manufactured***" or "***Manufacturing***" means any activity involved in or relating to the manufacturing, quality control testing (including in-process, release and stability testing), releasing or packaging, for pre-clinical and clinical purposes, of API or a Product in finished form.

"***Milestone Event***" means a Pre-Licensing Milestone Event or a Post-Licensing Milestone Event, as the case may be.

"***Minimum Third Party Payments***" means [***].

"***NAS Development Candidate***" has the meaning set forth in Section 2.1.1(b)(i).

"***NDA***" means a New Drug Application filed with the FDA after completion of Clinical Studies to obtain Approval for a Product in the United States.

"***NDA Approval***" means the Approval of an NDA by the FDA for a Product in the U.S.

"***Net Sales***" of a Product in a particular period will mean the amount calculated by subtracting from the Sales of such Product for such period: (A) a lump sum deduction of four percent (4%) of Sales under item (i) of the "*Sales*" definition in lieu of those deductions that are not accounted for on a Product-by-Product basis (e.g., freight, postage charges, transportation insurance, packing materials for dispatch of goods, custom duties); (B) uncollectible amounts accrued during such period based on a proportional allocation of the total bad debts accrued during such period; (C) credit card charges (including processing fees) accrued during such period on such Sales; and (D) government mandated fees and taxes and other government charges accrued during such period for such Product including, for example, any fees, taxes or other charges that become due in connection with any healthcare reform, change in government pricing or discounting schemes, or other action of a government or regulatory body; provided that the foregoing deductions under (A) to (D) were not already taken as a gross-to-net deduction in accordance with the then currently used International Financial Reporting Standards (IFRS) in the calculation of Sales of such Product for such period.

"***New Third Party Licenses***" has the meaning set forth in Section 8.3.2.

"***Non-Breaching Party***" means the Party that believes the Breaching Party is in material breach of this Agreement.

[***]

"***Omnibus Collaboration Patents***" has the meaning set forth in Section 7.1.3(a).

"***Option***" has the meaning set forth in Section 3.1.

"***Option Deadline***" has the meaning set forth in Section 3.1.

"***Option Period***" has the meaning set forth in Section 1.1.

"***Party***" or "***Parties***" means Roche and Isis individually or collectively.

"***Patent Costs***" means the reasonable fees and expenses paid to outside legal counsel, and filing, maintenance and other reasonable out-of-pocket expenses paid to Third Parties, incurred in connection with the Prosecution and Maintenance of Patent Rights.

"***Patent Rights***" means (a) patents, patent applications and similar government-issued rights protecting inventions in any country or jurisdiction however denominated, (b) all priority applications, divisionals, continuations, substitutions, continuations-in-part of and similar applications claiming priority to any of the foregoing, and (c) all patents and similar government-issued rights protecting inventions issuing on any of the foregoing applications, together with all registrations, reissues, renewals, re-examinations, confirmations, supplementary protection certificates, and extensions of any of (a), (b) or (c).

"***Permitted Licenses***" means (1) licenses granted by Isis before or after the Effective Date to any Third Party under the Isis Core Technology Patents, the Isis Manufacturing and Analytical Patents, or the Isis Manufacturing and Analytical Know-How (but not under the Isis Product-Specific Patents) to (a) use oligonucleotides (or supply oligonucleotides to end users) solely to conduct pre-clinical research, or (b) enable such Third Party to manufacture or formulate oligonucleotides, where Isis does not assist such Third Party to identify, discover or make a Compound or Product; and (2) material transfer agreements with academic collaborators or non-profit institutions solely to conduct noncommercial research. A list of relevant Permitted Licenses as of the Effective Date is set forth on APPENDIX 7 attached hereto.

"***Person***" will mean any corporation, limited or general partnership, limited liability company, joint venture, trust, unincorporated association, governmental body, authority, bureau or agency, any other entity or body, or an individual.

"***Phase 1 Trial***" means the initial clinical testing of a Product in humans (first-in-humans study) in any country that is designed to satisfy the requirements of 21 C.F.R. § 312.21(a) FDCA, as amended from time to time, or a foreign equivalent thereof.

"***Phase 1 Trial Data Package***" means the listing and tables of safety data (and early efficacy data if applicable) available to the Party conducting such Phase 1 Trial after the last patient receives his/her last dose of a Product in such Phase 1 Trial.

"***Phase 2 Trial***" means a human clinical study that is intended to explore a variety of dose and dose response to generate initial evidence of clinical safety and activity in a target patient population for which the primary endpoints include a determination of dose ranges and/or a preliminary determination of efficacy in patients being studied as described in 21 C.F.R. § 312.21(b) FDCA, as amended from time to time, or a foreign equivalent thereof.

"***Phase 2 Trial Data Package***" means, with respect to a given Phase 2 Trial, the listing and tables of safety and efficacy data available to Roche after the last patient has received his/her last dose of a Product in such Phase 2 Trial.

"***Phase 4 Trial***" means (i) any Clinical Study conducted to satisfy a requirement of a Regulatory Authority in order to maintain Approval, or (ii) any Clinical Study conducted after the first Approval in the same disease state for which a Product received Approval other than for purposes of obtaining Approval.

"***Post-Licensing Milestone Event***" has the meaning set forth in Section 6.4.

"***Pre-Clinical Studies***" means *in vitro* and *in vivo* studies of a Product, not in humans, including those studies conducted in whole animals and other test systems, designed to determine the toxicity, bioavailability, and pharmacokinetics of a Product and whether a Product has a desired effect.

"***Pre-Licensing Milestone Event***" has the meaning set forth in Section 6.2.

"***Prior Agreements***" means the agreements listed on SCHEDULE 8.2.7 attached hereto.

"***Proceeding***" means an action, suit or proceeding.

"***Product***" means a finished drug product containing as an active pharmaceutical ingredient (i) an Isis Development Candidate, or (ii) a Brain Shuttle Development Candidate.

"***Prosecution and Maintenance***" or "***Prosecute and Maintain***" means, with regard to a Patent Right, the preparing, filing, prosecuting and maintenance of such Patent Right, as well as handling re-examinations, reissues, and requests for patent term extensions with respect to such Patent Right, together with the conduct of interferences, the defense of oppositions and other similar proceedings with respect to the particular Patent Right. For clarification, "***Prosecution and Maintenance***" or "***Prosecute and Maintain***" will not include any other enforcement actions taken with respect to a Patent Right.

"***R&D Plan***" means either (i) the Isis Development Candidate-R&D Plan, or (ii) the Brain Shuttle Development Candidate-R&D Plan.

"***Receiving Party***" has the meaning set forth in Section 11.1.

"***Reduced Royalty Period***" has the meaning set forth in Section 6.7.2(d).

"***Reference Rate***" has the meaning set forth in Section 6.7.2(b).

"***Registration-Directed Trial***" means a pivotal Clinical Study (whether or not called a "*Phase 3*" Clinical Study) [***] intended to establish that a Product is safe and effective for its intended use; and is intended to support NDA filing (or foreign equivalent filing) of such Product in patients having the disease or condition being studied, as described in 21 C.F.R. § 312.21(c) FDCA, as amended from time to time, or a foreign equivalent thereof.

"***Registration-Directed Trial Data Package***" means, with respect to a given Registration-Directed Trial, the listing and tables of safety and efficacy data available [***].

"***Regulatory Authority***" means any governmental authority, including the FDA, EMA or Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto), that has responsibility for granting any licenses or approvals or granting pricing or reimbursement approvals necessary for the marketing and sale of a Product in any country.

"***Reviewing Entity***" means an institutional review board (IRB), research ethics board (REB), European ethical committee (EEC), or equivalent appropriate governmental ethical reviewing entity responsible for approving an entity to participate in a Clinical Study as a clinical site.

"***RMC***" means Isis' Research Management Committee, or any successor committee.

"***Roche***" has the meaning set forth in the Preamble of this Agreement.

"***Roche Collaboration Know-How***" means Know-How discovered, developed, invented or created solely by or on behalf of Roche or its Affiliate or a Third Party acting on their behalf in the performance of an R&D Plan, that is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Roche Collaboration Patents***" means Patent Rights discovered, developed, invented or created solely by or on behalf of Roche or its Affiliate or a Third Party acting on their behalf in the performance of an R&D Plan, that are necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Roche Collaboration Technology***" means Roche Collaboration Know-How, Roche Collaboration Patents and Roche's interest in any Jointly-Owned Collaboration Technology and Brain Shuttle Collaboration Patents.

"***Roche Existing Brain Shuttle Patents***" has the meaning set forth in Section 8.4.1. A list of Roche Existing Brain Shuttle Patents as of the Effective Date is set forth on SCHEDULE 8.4.1 attached hereto.

"***Roche Full Royalty***" has the meaning set forth in Section 6.7.1.

"***Roche Know-How***" means any Know-How that (i) did not arise in connection with the performance of an R&D Plan, (ii) is owned, used, developed by, or licensed to Roche or its Affiliates, and (iii) is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field, in each case to the extent Controlled by Roche or its Affiliates on the Effective Date or at any time during the Agreement Term.

"***Roche Patents***" means any Patent Rights that (i) did not arise in connection with the performance of an R&D Plan, (ii) are owned, used, developed by, or licensed to Roche or its Affiliates, and (iii) are necessary or useful to Develop, Manufacture or Commercialize a Product in the Field, in each case to the extent Controlled by Roche or its Affiliates on the Effective Date or at any time during the Agreement Term.

"***Roche-Prosecuted Patents***" has the meaning set forth in Section 7.2.4.

"***Roche Reduced Royalty***" has the meaning set forth in Section 6.7.2(b).

"***Roche R&D Activities***" means the research, pre-clinical and/or clinical activities for which Roche is designated as responsible under an R&D Plan.

"***Roche Supported Pass-Through Costs***" means the [***].

"***Roche-Selected Brain Shuttle Development Candidate***" means that as between a given Isis Development Candidate and a given Brain Shuttle Development Candidate, in accordance with Section 5.1.1, the Independent Expert did not recommend that such Brain Shuttle Development Candidate be progressed into Phase 2 Trials.

"***Roche Technology***" means Roche's interest in Roche Collaboration Technology, Roche Know-How, Roche Patents and any trademarks described in Section 4.1.7, owned, used, developed by, or licensed to Roche or its Affiliates that is necessary or useful to Develop, Manufacture or Commercialize a Product.

"***Royalty Quotient***" has the meaning set forth in Section 6.7.2(b).

"***Sales***" of a Product in a particular period will mean the sum of (i) and (ii):

> **(i)** the amount stated in Roche sales line of its externally published audited financial statements with respect to such Product for such period (excluding sales to any Sublicensee that are used for research or Development or re-sold by such Sublicensee as sales under item (ii) below). This amount reflects the gross invoice price at which such Product was sold or otherwise disposed of (other than for use as clinical supplies or free samples) by Roche/Genentech, its Affiliates and Group Sublicensees to Third Parties (excluding sales to any Sublicensee that are used for research or Development or re-sold by such Sublicensee as sales under item (ii) below) in such period reduced by gross-to-net deductions, if not previously deducted from such invoiced amount, taken in accordance with the then currently used International Financial Reporting Standards (IFRS).

By way of example, the gross-to-net deductions taken in accordance with International Financial Reporting Standards (IFRS) as of the Effective Date include the following:

(a) credits, reserves or allowances granted for (w) damaged, outdated, returned, rejected, withdrawn or recalled Product, (x) wastage replacement and short-shipments, (y) billing errors and (z) indigent patient and similar programs (e.g., price capitation);

(b) governmental price reductions and government mandated rebates;

(c) chargebacks, including those granted to wholesalers, buying groups and retailers;

(d) customer rebates, including cash sales incentives for prompt payment, cash and volume discounts; and

(e) taxes, duties and any other governmental charges or levies imposed upon or measured by the import, export, use, manufacture or sale of a Product (excluding income or franchise taxes).

For the purpose of clarity, sales by Roche/Genentech and its Affiliates to any Sublicensee and/or Group Sublicensee that are used for research or Development or re-sold by such Sublicensee or Group Sublicensee as sales under item (ii) below will be excluded from "*Sales*" calculated under this item (i).

(ii) Sublicensee (excluding Compulsory Sublicensee) sales amounts reported to Roche and its Affiliates in accordance with Sublicensee contractual terms and their then currently used accounting standards. For the purpose of clarity, any Sublicensee sales as reported to Roche in accordance with Compulsory Sublicense agreements will be excluded from the Sales amount.

"***SNP***" means single nucleotide polymorphism.

"***Specific Performance Milestone Event***" has the meaning set forth in the definition of "*Commercially Reasonable Efforts*."

"***Step-In Party***" has the meaning set forth in Section 7.4.1.

"***Sublicensee***" means a Third Party to whom a Party or its Affiliates or Sublicensees has granted a sublicense or license under any Licensed Technology or Roche Technology, as the case may be, licensed to such Party in accordance with the terms of this Agreement.

"***Third Party***" means a Person or entity other than the Parties or their respective Affiliates.

"***Third Party Obligations***" means any financial and non-financial encumbrances, obligations, restrictions, or limitations imposed by an agreement between Isis and a Third Party (including the Isis In-License Agreements) that relate to a Product, HTT, including field or territory restrictions, covenants, milestone payments, diligence obligations, sublicense revenue, royalties, or other payments.

"***United States***" or "***U.S.***" means the fifty states of the United States of America and all of its territories and possessions and the District of Columbia.

"***UTSW Agreement***" means that certain Exclusive Patent License Agreement between Isis and the University of Texas Southwestern Medical Center at Dallas dated June 24, 2010.

"***Valid Claim***" means a claim (i) of any issued, unexpired United States or foreign Patent Right, which will not, in the country of issuance, have been donated to the public, disclaimed, nor held invalid or unenforceable by a court of competent jurisdiction in an unappealed or unappealable decision, or (ii) of any United States or foreign patent application within a Patent Right, which will not, in the country in question, have been cancelled, withdrawn, abandoned nor been pending for more than seven (7) years, not including in calculating such seven-year period of time in which such application is in interference or opposition or similar proceedings or time in which a decision of an examiner is being appealed. Notwithstanding the foregoing, on a country-by-country basis, a patent application pending for more than seven years will not be considered to have any Valid Claim for purposes of this Agreement unless and until a patent meeting the criteria set forth in clause (i) above with respect to such application issues.

APPENDIX 2

Isis Development Candidate-R&D Plan

[***]

APPENDIX 3

Brain Shuttle Development Candidate-R&D Plan

[***]

APPENDIX 4

Isis Development Candidate Checklist

[***]

APPENDIX 5

Roche's Development and Commercialization Activities and Specific Performance Milestone Events

[***]

APPENDIX 6

Brain Shuttle Collaboration Patents

[To be added/updated during Agreement Term]

APPENDIX 7

Relevant Permitted Licenses as of the Effective Date

[***]

SCHEDULE 1.5.1

JSC GOVERNANCE

(a) One of the primary purposes of the JSC is to empower the JSC to make decisions with respect to the composition and conduct of the R&D Plans that are not specifically vested in a Party under this Agreement. Nothing in this SCHEDULE 1.5.1 is intended to affect any decision-making authority granted to a Party in the body of the Agreement.

(b) The JSC will begin on the Effective Date and will dissolve upon the first Approval; *provided*, *however*, that Isis' obligation to participate in the JSC will terminate upon Option exercise. Thereafter, Isis will have the right, but not the obligation, to participate in JSC meetings.

(c) The JSC will determine the JSC operating procedures, including frequency of meetings (at least quarterly prior to Option exercise and at least yearly after Option exercise), location of meetings, and responsibilities for agendas and minutes. The JSC will codify these operating procedures in the written minutes of the first meeting.

(d) The JSC may hold meetings in person or by audio or video conference as determined by the JSC; but at least two meetings per year will be in person (one held at Isis' facilities, and the other held at Roche's facilities). Alliance Managers will attend JSC meetings as participating non-members. In addition, upon prior approval of the other Party, each Party may invite its employees or consultants to attend JSC meetings, including any subject matter expert(s) with valuable knowledge of HTT or Huntington's Disease.

(e) The chairperson will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that JSC meetings occur, JSC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 1.5.2, Section 7.1.3 and Section 12.1, as applicable.

(f) The JSC members from the same Party will collectively have one vote. The JSC will strive to make recommendations with approval of both Isis members and Roche members, and record such recommendations in the minutes of the applicable JSC meeting.

(G) The JSC may form subcommittees and working groups as it determines in order to carry out its activities under this Agreement, all of which will dissolve when the JSC dissolves.

(h) Without limiting the provisions of Section 1.5.1, subject to Section 1.5.2, the JSC will perform the following functions:

(i) advise on the details and deliverables for the selection of Development Candidates;

(ii) review the overall progress of efforts to select Development Candidates;

(iii) review emerging data and consider changes to the R&D Plans;

(iv) review, provide advice and recommend revisions to the R&D Plans

(v) discuss the selection of the Brain Shuttle Development Candidate;

(vi) materially amend the R&D Plans upon the JSC's unanimous written consent;

(vii) record recommendations and decisions of the JSC in the JSC's meeting minutes;

(viii) such other review and advisory responsibilities assigned to the JSC pursuant to this Agreement; and

(ix) discuss whether to continue with Change Overruns.

SCHEDULE 1.5.3

Alliance Management Activities

Each Alliance Manager is responsible for:

(a) Promoting the overall health of the relationship between the Parties;

(b) Developing a mutually agreed alliance launch plan covering any activities and systems that the Parties need to implement within the first one hundred (100) days after the Effective Date to support the R&D Plans;

(c) Organizing JSC meetings, including agendas, drafting minutes, and publishing final minutes;

(d) Supporting the co-chairs of the JSC with organization of meetings, information exchange, meeting minutes, and facilitating dispute resolution as necessary;

(e) Preparing status and progress reports on the above as determined necessary by the JSC;

(f) Ensuring compliance in maintaining the Isis Internal ASO Safety Database as outlined in Section 5.2.2;

(g) Ensuring proper approval of publications prior to submission as required in Section 11.4; and

(h) Understanding and communicating the components contained in the relationship-management document provided by Isis to Roche, to assist Roche in understanding and complying with the contractual obligations under the Isis In-License Agreements after Option exercise.

SCHEDULE 1.6.2(b)(i)

Cost of ASOs Supplied Under the Brain Shuttle Development Candidate-R&D Plan

[***]

SCHEDULE 1.7.1

Isis' Fully Absorbed Cost of Goods Methodology
Cost Estimate of API Cost per Kilogram
(OOO's)

[***]

SCHEDULE 6.7.2(e)

Royalty Calculation Examples

[***]

SCHEDULE 6.7.2(f)

Allocation of Net Sales

[***]

SCHEDULE 6.11.1

Isis In-License Agreements

(Relevant to Compounds as of the Effective Date)

[***]

SCHEDULE 8.2.4(a)

Isis Core Technology Patents

[***]

SCHEDULE 8.2.4(b)

Isis Manufacturing and Analytical Patents

[***]

SCHEDULE 8.2.4(c)

Isis Product-Specific Patents

[***]

SCHEDULE 8.2.7

Prior Agreements

[***]

SCHEDULE 8.4.1

Roche Existing Brain Shuttle Patents

[***]

EXHIBIT 31.1

CERTIFICATION

I, Brett P. Monia, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Ionis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this quarterly report;

3. Based on my knowledge, the condensed consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, condensed consolidated results of operations and condensed consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: May 3, 2023

/s/ BRETT P. MONIA
Brett P. Monia, Ph.D.
Chief Executive Officer

EXHIBIT 31.2

CERTIFICATION

I, Elizabeth L. Hougen, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Ionis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this quarterly report;

3. Based on my knowledge, the condensed consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, condensed consolidated results of operations and condensed consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: May 3, 2023

/s/ ELIZABETH L. HOUGEN
Elizabeth L. Hougen
Chief Financial Officer

Exhibit 32.1

CERTIFICATION

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, Brett P. Monia, the Chief Executive Officer of Ionis Pharmaceuticals, Inc., (the "Company"), and Elizabeth L. Hougen, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Quarterly Report on Form 10-Q for the period ended March 31, 2023, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Periodic Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Periodic Report and the results of operations of the Company for the period covered by the Periodic Report.

Dated: May 3, 2023

/s/ BRETT P. MONIA
Brett P. Monia, Ph.D.
Chief Executive Officer

/s/ ELIZABETH L. HOUGEN
Elizabeth L. Hougen
Chief Financial Officer

A signed original of this written statement required by Section 906 has been provided to Ionis Pharmaceuticals, Inc. and will be retained by Ionis Pharmaceuticals, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.